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THE RELATION OF THE INTERNAL SECRETIONS TO TUMOR METABOLISM*

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Various glands of internal secretion exert a profound influence upon the growth and metabolism of the normal intact organism. Their possible influence upon the growth of abnormal tissue structures, such as tumors, has been receiving increasing attention while their possible influence upon tumor metabolism has been largely ignored. This subject offers interesting possibilities because transplanted tumors are essentially parasitic tissue, connected with the host practically only by blood supply. They have no function, essential to the host, which might be stimulated. They consist of constant cell structure which does not mutate, and have a relatively constant and characteristic metabolism. Transplanted tumors, therefore, offer interesting opportunities for metabolic investigations, particularly in the study of isolated tissues.

The measurement of the effect of various endocrines upon isolated tissues has been made by Foster (1), Dresel (2), Anselmino, Eichler and Schlossman (3), McEachern and Andrus (4), Hopping (5), Davis and Hastings (6), and others. They have noted distinct effects upon various normal tissues. In our work, by similar methods, the effect of the internal secretions upon tumor metabolism has been studied, using thin slices of tissue and at the same time, for comparison, making the same determinations upon a normal tissue from the host of that tumor.

Aside from the primary aim of obtaining data relative to the effect of the hormone upon the tumor metabolism, this method might give information regarding the mechanism of hormone action for it might be presumed that the hormone was acting through the blood stream rather than by nerve stimulation, since the transplanted tumor has virtually no nerve supply.†

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†It is true that Oertel, Nye, and Tomlinson (7) have demonstrated nerve fibers in spontaneous human breast tumors, but no satisfactory demonstration of this has yet been made in transplanted subcutaneous tumors (8).

PROCEDURE

Hormones were administered subcutaneously to tumor-bearing mice or one of the glands of internal secretion was removed. In all instances the injections were made distant from the tumor site. The effects of these procedures upon the metabolism of a tumor transplanted to mice were noted. The determinations were made in all instances with the Warburg modification of the Haldane-Barcroft blood gas apparatus. By the methods described by Warburg (9), it is possible to determine the oxygen consumption and carbon dioxide production of respiration and the anaerobic glycolysis of excised tissues with sufficient accuracy for our purpose. The details of the method are also well described by Richardson (10) and we have followed closely the method he outlines.

There is an average difference of not over 5 per cent for the oxygen consumption measurements in consecutive duplicate experiments, whereas the average variation is about 10 per cent for carbon dioxide figures, aerobically and anaerobically. Thus, the respiratory quotient is distinctly less reliable than the oxygen consumption and consequently is of less significance, except in cases in which a consistent change of considerable magnitude exists. However, the similarity of the average figures in different groups of controls, despite the variation in individual experiments, is surprisingly constant.

The tissues studied were mouse sarcoma No. 180, and the liver of the same mouse, which served as the normal tissue control. They were removed from the mouse as soon as it was killed, and the experiments were assembled as rapidly as possible. The aerobic determinations were made in Ringer phosphate solution containing 0.20 per cent glucose, and all the anaerobic determinations in Ringer's solution containing 0.15* per cent glucose and 0.20 per cent sodium bicarbonate. Both solutions were adjusted to between pH 7.3 and 7.5. The determinations of the gas consumption and production were made over a period of one to two hours, most of them for one hour. The manometers were first stabilized by being shaken in the water bath, regulated to 37.5° C., for twenty minutes. Readings were made at ten-minute intervals. Respiration for the anaerobic experiments was inhibited with a mixture of 95 per cent nitrogen and 5 per cent carbon dioxide gas.

The animals used were inbred, pure-strain, tumor-susceptible, black mice.§ The age of the mice at the time of the experiments ranged between three and fifteen months, by far the greater number being four to eight months old.

The tumors, which grow rapidly in over 90 per cent of the implantations, reach a satisfactory size for experimental purposes in two or three weeks. In these experiments, we have usually used tumors two to four

*Several duplicate anaerobic experiments with 0.20 per cent glucose showed the carbon dioxide production to be about 10 per cent higher than in a solution with 0.15 per cent glucose.

§Inbred, pure-strain, white mice were used for some of the thyroidectomies.

weeks old. At this age they are ordinarily of good size and the degree of necrosis is not great so that sufficient good healthy tissue is available.

The hormones studied were thyroxin, thymus extract (Karkinolysin),† insulin, anterior pituitary extract (Prolan),† and Hartman's extract of the adrenal cortex (Cortin),† each being administered to distinct groups of mice. All were given subcutaneously and at a site distant from the tumor implants. The thyroid, gonads, and suprarenal glands have been removed from other groups. All operated animals were permitted to go a minimum period of one month after operation, usually more than two months, before being used for an experiment. Control determinations upon uninjected mice were gradually accumulated during the observations on the experimental animals.

RESULTS

In this summarizing communication, the results in detail for each group of experiments and the details of dosage and surgical procedure will not be given. The general policy has been to give very large doses of extracts in order to be certain of obtaining an effect and, where glands

TABLE I.

DUPLICATE EXPERIMENTS (CONTROL ANIMALS). NON-FASTING.

Date	Tumor			Date	Liver		
	QO_2	QCO_2	R. Q.		QO_2	QCO_2	R. Q.
6/ 2/30	−7.1	+5.0	0.70	10/25/30	−12.5	+9.0	0.72
	−6.7	+4.9	0.74		−12.5	+9.3	0.75
6/ 4/30	−6.3	+7.5	1.19	10/28/30	−10.4	+6.5	0.62
	−6.0	+4.4	0.73		− 9.3	+5.5	0.59
6/ 9/30	−5.4	+4.4	0.82	11/12/30	−8.0	+4.2	0.53
	−5.5	+3.5	0.64		−7.7	+5.0	0.65
7/ 2/30	−7.1	+6.4	0.90	11/22/30	−9.0	+8.7	0.96
	−7.9	+6.3	0.80		−8.0	+8.0	1.01
8/ 7/30	−8.3	+7.5	0.91	11/26/30	−6.9	+5.5	0.81
	−7.8	+6.0	0.77		−7.0	+5.1	0.73
9/ 9/30	−7.5	+7.2	0.96				
	−7.6	+6.1	0.81				
10/ 3/30	−9.6	+7.8	0.82				
	−8.2	+8.3	1.00				
10/ 7/30	−7.8	+6.2	0.79				
	−7.9	+7.2	0.91				
Average.....	−7.3	+6.2	0.85	Average.....	−9.1	+6.7	0.73

QO_2—Cubic millimeters of oxygen consumed per milligram of tissue, dry weight, per hour.
QCO_2—Cubic millimeters of carbon dioxide produced per milligram of tissue, dry weight, per hour.
R. Q.—Respiratory quotient.
The symbols have the same significance in all subsequent tables.

†We wish to take this opportunity to thank Dr. Frank Hartman for a supply of his active extract of the adrenal cortex and the Winthrop Chemical Co. for their generosity in supplying their ovary stimulating Prolan, which was active as demonstrated on immature mice. The thymus extract was kindly furnished by Dr. Adolph Hanson, but its activity we could not determine.

have been extirpated, each animal has been carefully autopsied to be certain that the removal of the particular organ has been complete.

The results, in duplicate experiments on normal controls, are shown in Table I, to give an indication of the accuracy of the observations.

Most of the experiments have been made upon fasting animals. However, separate control series upon fasting and non-fasting animals have been made. The average and usual fasting time has been between fourteen and nineteen hours, throughout. A composite table of averages for experiments is here given. Three of the experiments with Prolan were made upon non-fasting animals but as the results were not strikingly different in this instance, they are combined with the fasting.

Study of this table shows some changes but no very striking demonstrable effects upon the respiratory metabolism from extirpation of any gland or administration of any of the hormones. After Prolan and Cortin, the respiratory quotient was consistently low for liver. The low tumor QO_2 after Cortin is suggestive but the decrease is not very great.

The results of individual experiments after suprarenalectomy were inconstant. However, there appeared to be no effect upon tumor metabolism and a slightly depressing effect upon liver metabolism.

Thyroidectomy produced a low liver and tumor metabolism but this was more apparent than real for the metabolism of both was not depressed in five of the ten observations. The reason for this failure to produce more constant hypothyroidism is probably because the thyroid is very small and the parathyroids, in close approximation, are invisible. When thyroidectomy is done, it is complicated by simultaneous parathyroidectomy and unless calcium and parathormone are given after the operation the mice, practically without exception, develop tetany and die.

The first group of orchidectomies must be compared with the non-fasting controls. In both groups the oxygen consumption for tumor was lower than normal. This result, though suggestive, must be interpreted with caution because of failure to find simultaneous, distinctly decreased, liver metabolism. The low anaerobic glycolysis of tumor after orchidectomy was not confirmed in the second group and, therefore, this finding is probably not significant.

The anaerobic glycolysis was not constantly and significantly changed in any group, excepting when insulin was administered. Here the tumor $Q\frac{N_2}{CO_2}$ was distinctly below normal and this result was quite constant in 7 of the 8 experiments. The explanation for this result is not clear. Probably, repeated induction of hypoglycemia, during the days of insulin administration before the experiment, is the important factor. Each mouse in this group had distinct hypoglycemia when killed for the experiments. Details of this phase of the work are reported elsewhere (11).

Thyroxin: The results of the administration of thyroxin appear to be significant and important. They are, therefore, discussed here in greater detail.

TABLE II.

TABLE OF AVERAGES AFTER HORMONES AND AFTER EXTIRPATION OF GLANDS.

Type	Number of Exp.	Daily Dose	Number of Days Given	Average Period of Fast (Hours)	Average Post-Operative Period (Days)	Tumor				Liver			
						QO_2	QCO_2	R. Q.	$Q^{N_2}_{CO_2}$	QO_2	QCO_2	R. Q.	$Q^{N_2}_{CO_2}$
Controls	24			18		−7.1	+6.1	0.85	+20.8 (21 exp.)	−10.1	+6.7	0.66	+2.4 (22 exp.)
	18			0		−8.3	+7.6	0.92	+19.4	−8.6	+6.3	0.73	+2.9
Insulin	13 tumor 14 liver	0.5 to 4 units	1–70	2–3		−7.6	+6.5	0.86	+14.6 (8 exp)	−9.4	+6.8	0.72	+1.9 (11 exp.)
Prolan	9	0.2 cc. (10 units)	9—18	12		−7.3	+6.7	0.92	+21.4	−9.1	+5.4	0.59	+1.9
Cortin	10	0.5 cc. b. i. d.	5–15	18		−6.6	+5.2	0.80	+21.4	−9.8	+5.4	0.55	+2.2
Thymus Extract (Karkinolysin)	8	0.2 to 0.4 cc.	35–66	10		−7.7	+6.4	0.83	+19.0	−10.2	+6.8	0.67	+3.0
Thyroidectomy	10			21	94	−6.0	+5.4	0.90	+19.8	−8.6	+6.3	0.73	+3.1 (9 exp.)
Suprarenalectomy	12			17	81	−6.8	+5.6	0.82	+22.2	−8.8	+5.4	0.61	+2.8
Orchidectomy Group I	7 tumor 9 liver			1–2	107	−7.1	+4.9	0.69	+14.7 (6 exp.)	−8.0	+5.9	0.74	+2.4 (8 exp.)
Group II	*7			16	112	−6.1	+5.3	0.87	+19.4				

*Six of the seven experiments were in duplicate.

$Q^{N_2}_{CO_2}$—Cubic millimeters of carbon dioxide produced anaerobically per milligram of tissue, dry weight, per hour.

TABLE III.

TABLE OF AVERAGES FOR METABOLISM OF ISOLATED TISSUES AFTER THYROXIN.

Type	Number of Exp.	Daily Dose	Days Given	Average Period of Fast (Hours)	Tumor				Liver			
					QO_2	QCO_2	R. Q.	$Q^{N_2}_{CO_2}$	QO_2	QCO_2	R. Q.	$Q^{N_2}_{CO_2}$
Controls	24			18	—7.1	+6.1	0.85	+20.8 (21 exp.)	—10.1	+6.7	0.66	+2.4 (22 exp.)
Alkali Injected	11 tumor* 13 liver	0.04 mg.	10–23	17	—7.3	+6.4	0.88	+24.9 (10 exp.)	—9.8	+6.6	0.67	+2.9 (12 exp.)
Thyroxin	27	0.01 to 0.2 mg.	3–51	18	—6.0	+5.6	0.93	+21.1 (24 exp.)	—12.0	+7.6	0.63	+3.0 (24 exp.)
Non-fasting Controls	18			0	—8.3	+7.6	0.92	+19.4	—8.6	+6.3	0.73	+2.9
Non-fasting Thyroxin	14	0.01 to 0.04 mg.	10–34	0	—7.0	+7.6	1.09	+21.0	—10.9	+8.4	0.77	+4.0

*Tumor $Q^{N_2}_{CO_2}$ very high in three experiments.

Crystalline thyroxin (Squibb) in dilute alkaline solution was administered to the mice, subcutaneously, in daily dosages varying from 0.2 to 0.01 milligram for periods ranging from 3 to 51 days. Most of the mice received 0.02 or 0.04 milligram for periods of 8 to 15 days, as this seemed to produce optimum results. During the period of thyroxin administration the mice were very well fed, food being present in the cage practically all of the time. The mice became thin and more active than normal while receiving thyroxin.

The tumors were usually implanted before thyroxin administration was commenced, and the majority were 16 to 21 days old at the time the metabolic observations were made. Tumors of the same age were used in the controls. The control mice in these experiments, as in all others, were of the same strain and kept under the same conditions as the injected group.

A small number of mice were injected with 0.04 milligram of sodium hydroxide in dilute solution daily for 10 to 20 days and these mice served as further controls, for the amount of alkali given was equivalent to the amount in the thyroxin solution of 0.04 milligram concentration. The average fasting period for these mice was 17 hours.

The results are shown in Table III. This gives average figures for the thyroxin injected and control mice in both the fasting and non-fasting groups.

Following thyroxin injections, there was a distinct increase in the oxygen consumption of liver tissue. This average increase was over 20 per cent above the normal. This increase was not invariable but occurred in the large majority of observations (76 per cent). The higher QO_2 results were found in the fasting group but the percentage increase over the controls was approximately the same as in the non-fasting. The respiratory quotients were not affected. The anaerobic glycolysis for the liver was strikingly increased.

The results for liver after thyroxin injections might, perhaps, have been anticipated. Surprising, however, was the effect upon the tumor metabolism. Here, in 19 out of 27 fasting animal experiments, there was distinct decrease in the oxygen consumption after thyroxin. The others fell within the normal range with only five distinctly higher than the average of all controls. In no instance was there a QO_2 higher than that not infrequently found for the normal. The average QO_2 for all 27 experiments was approximately 15 per cent below the normal. As a result of the QO_2 depression, the respiratory quotient was increased; the amount of carbon dioxide actually produced was within the range of normal. The results in the non-fasting group of mice were similar with depression of the oxygen consumption in 11 of the 14 experiments.

The anaerobic glycolysis for the thyroxin tumors was increased to a very slight, insignificant degree. The possibility of the aerobic glycolysis being increased to compensate for the decrease in oxygen consumption of

the tumor was considered and ruled out by ten controlled determinations upon thyroxin injected mice, using the bicarbonate method described by Negelein (12).

The total metabolism of eight mice was determined by Dr. William T. Salter, before and after thyroxin administration, with the open circuit method, using Carpenter's modification of the Haldane apparatus for gas analysis. The increase in the metabolism of the intact animal corresponded to the increase in the isolated liver tissue.

Some of the tumors were examined microscopically by Dr. Shields Warren and he noted no significant difference in those obtained from control or thyroxin injected mice. The number of mitotic figures was approximately the same in both.

Because it was thought that this sarcoma might be a tumor peculiar in its response to thyroxin, seven black mice bearing carcinoma No. 63 were each given subcutaneous injections of 0.02 milligram of thyroxin for 7 to 14 days and the tissue metabolism of the fasting animals was then measured. Each experiment was controlled by an uninjected fasting mouse bearing a similar tumor. The results closely resemble the results found in the sarcoma experiments. The detailed data of these observations may be found in another paper (13).

SUMMARY

1. Administration of anterior pituitary extract, extract of the adrenal cortex and thymus extract in vivo, did not strikingly affect the metabolism of isolated mouse sarcoma tissue. After insulin the tumor anaerobic glycolysis was decreased.

2. The removal of the suprarenal glands produced no constant effect upon the metabolism of this parasitic tissue.

3. The results after orchidectomy were suggestive: the tumor oxygen consumption was consistently low, though the liver of the host was not strikingly affected.

4. The average metabolism of both tumor and liver was depressed after thyroidectomy, but the results in individual experiments were not constant enough to permit the attachment of much significance to this finding before further experiments are done.

5. The administration of thyroxin in vivo produced an average increase of more than 20 per cent in the metabolism of isolated liver tissue and an appreciable decrease in the oxygen consumption of transplanted mouse tumors, sarcoma and carcinoma.

6. The aerobic and anaerobic glycolysis of the tumors was not significantly affected by thyroxin administration. The liver anaerobic glycolysis was increased.

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A CASE OF BILATERAL ADRENAL CYSTS

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As tumors and cysts of the adrenals are comparatively rare and, as far as I know, have never been diagnosed before in vivo by means of x-ray examination, a case of this kind will probably be of some interest.

Rolleston found adrenal metastases in 15 of 144 cases of malignant tumors elsewhere in the body. Le Dentu found metastases to the adrenals in 10 of 36 cases of carcinomatosis. Amongst the many autopsies I have attended I have seen only one case of a malignant tumor of the adrenals, a sarcoma of one gland. This patient died with sarcomatosis of the spinal cord; the adrenal sarcoma was taken to be the primary tumor.*

Primary adrenal tumors were previously taken to be extremely rare. In 1895, Williams stated that in 13,824 cases of tumors observed in the hospitals of London there was only one instance of a tumor of the adrenal (adenosarcoma). In 1898, however, Robert was able to gather 30 cases of adrenal tumors and 6 years later Hartman and Lècené reported 22 cases. Gradually, with the increasing interest in the endocrine glands, such instances have been reported in increasing numbers. Yet it is still a rare disease.

The tumors that have been observed in the adrenals have been: sarcoma, fibroma, neuroma, glioneuroma, glioma, lipoma, myoma, osteoma (extremely rare), lymphoma, angioma, lymphangioma, cysts, and echinococci.

True parenchymatous tumors have been: cortical adenoma and epithelioma, hypernephroma†, paraganglioma, etc. Amongst other adrenal diseases must be mentioned: tuberculosis, syphilis, actinomycosis (very rare), and certain tropical diseases (Trypanosoma Bruci, Spirochaete Duttoni, et al.).

The adrenal cysts reported cover tumors of most varying nature. The echinococcus cysts are found in the adrenals themselves. The other cysts may be divided into 4 groups: true glandular cysts, cystic adenoma, cystic lymphangioma and pseudocysts. The last mentioned are merely cavities filled with blood and broken down tissue elements, resulting from haemorrhage, suppuration or broken down new-growth.

True glandular cysts or retention cysts are rare. As a rule, they are small and lined with cylindrical epithelium. They are found most frequently in animals, very seldom in man. Thus Rolleston has only one case of this kind in his material. The embryonic cysts are also small, as a rule, and lined with ciliated cylindrical epithelium (Sick, 1903). Their origin is explained as due to an intraglandular retention of the Wolffian ducts.

Cystic adenoma is a little more frequent (Marchand, Askanazi, Manasse, Kelly, Kelynach).

The lymphangioma cysts, which are also called serous cysts, are of some surgical interest, as they may attain to enormous dimensions. Their development is slow and progressive, most often unilateral, but now and then bilateral (Christie, Vecchi). In 1910, the latter author had collected 10 cases of this kind. In 1912, Nowicki reported some additional cases.

Finally, cystic degeneration of the adrenals is encountered occasionally, being of the same nature as, for example, cystic degeneration of the kidneys. Something of the kind was found by Lefèvre in a patient suffering from Addison's disease, in which case the adrenals were so full of small serous cysts that only a little remnant of the normal adrenal tissue was left.

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*Reported in Neurologisk Selskabs Forhandlinger.

†The dissertation by Johannes Ipsen treats in part of this type of tumor.

CASE REPORT

My patient was a single woman, aged 40, a telephone operator.

April 17-July 27, 1924, she was under treatment in Department D, Frederiksberg Hospital, under the diagnosis: Mental depression; pluriglandular dysfunction (pituitary, thyroid, parathyroid, and adrenal).

The mother and one sister have goiter, and the whole family is said to be very nervous. The patient was born in Jämteland (Sweden) and she has never been farther north (never in Iceland). Her menses have always been normal and regular. There has been no demonstrable psychic trauma.

She had been a telephone operator since 1915, and during these years she had been reported ill only now and then, although she had suffered ever since her earliest youth from attacks of gnawing pains in the top of the head, and pains of the neck which have been designated as globus sensations. She has had frequent attacks of nausea and vomiting, and she had been told she had hyperacidity.

During the year before her admission to the hospital she had been indisposed and incapable of working. A three-months' vacation did not improve her condition. In addition to the marked fatigue, she complained of depression, attacks of anxiety and uncontrolled lacrimation, which came most often in nocturnal attacks accompanied by marked palpitation of the heart.

The *physical examination* failed to reveal any particular abnormality of the nervous system apart from a little hypaesthesia of the left leg. There were noted exophthalmos and doubtful Gräfe, negative Moebius and negative Stellwag signs. The pulse rate was irregular, sometimes 70, sometimes above 100. There was a distinct tremor of the hands and the tongue. The thyroid felt enlarged, especially on the sides. The neck/wrist ratio was 37/17 cm. The hair growth of the head and eyebrows was normal, as were the pupils. There were positive Chvostek, Hoffmann, Trousseau and Erb signs. The weight was 81.5 kgm; the height, 172 cm. The patient was corpulent and the abdomen particularly large. The haemoglobin was 80 per cent (Sahli). An Ewald test meal gave the following results: (1) (1 hour) 20+8 cc., 45/48 (?); (2) (1 hour) 110 cc., 57/75; mucus, +; poor chymefaction. The blood pressure (systolic) was 125 mm.; the basal metabolism, 89 per cent.

X-ray examination of sella turcica: The sella did not appear to be enlarged. Its posterior border was not sharply defined; the continuity of this outline appeared as if broken and some of the bone tissue absorbed. The x-ray plate is suggestive of some pathological process that may have produced these changes in the appearance of the sella, but nothing definite can be said in this respect.

Eye examination disclosed no abnormalities.

Otologic examination gave normal findings. No evidence of otogenous factors in her condition could be detected.

On admission she did not seem to be depressed to any particular degree, but in the hospital she had several attacks of depression, and a few of these were accompanied by dizziness. As a rule, these attacks were associated with the menses, but she had the most severe attack when she was discharged from the telephone company. Now and then she had an attack at night, accompanied by "twitching" of the face and arms. She was treated with thyroidin, suprarenin, calcium, bromide, and medinal; finally, she was transferred from the hospital for convalescence in the country.

Second Hospital Treatment, Feb. 12-Aug. 1, 1931. She had not been quite well since her previous stay in the hospital. She was always somewhat depressed and cried readily, but now she thought this depression and tendency to weeping were due to economical troubles, as she and a girl friend she was living with had to make out on about twenty-five dollars a month.

She did not sleep well, partly on account of her depressive trend of thought, partly because she was frequently awakened by attacks of difficulty in breathing; pains over the precordium and sensation of oppression of the chest. She further complained of headache, dull pains and twitching of the left half of the face. Now and then she had a fainting fit, but no convulsions. She often had nausea, dyspeptic discomfort and vomiting after meals (sometimes a little blood-tinged). She was always hungry, and yet her appetite was poor. She had difficulty in urinating, with frequent attacks of tenesmus. The menses, which had been regular before, had now become irregular, occurring at intervals of 2-5 weeks, lasting 3 days and preceded by pains.

Neurological examination: Apart from a slight accentuation of the tendon reflexes all the findings were practically normal.

There was distinct exophthalmos; Gräfe, +; Moebius, —; Herthoge, +; Chvostek +; Hoffmann, +; Erb, +. Neck/wrist ratio, 41/17.5 cm. Standard metabolism was 89 per cent; blood calcium, 8.6 mgm. per cent.

The blood pressure was (1) 180/100; (2) 140/80; (3) 120/85. The haemoglobin was 80 per cent (Sahli). The blood sugar (fasting), 0.098 per cent. The uric acid content of the blood was 3.3 mgm. per cent. The red corpuscles were 4,250,000 and white corpuscles, 6640.

Auscultation of the heart and lungs showed no abnormalities. The abdomen was large but soft (the weight of the patient was 93 kgm.). The knees showed some small patches or psoriasis.

During her stay in the hospital the patient gave the impression of a more marked inhibition and depression than when she had been here seven years before, and she still cried very readily. While in the hospital she had an attack of cystitis, which was treated with lapis lavage, pyelol and calcium.

One day she complained of pains over the lungs. With a view to the possibility of a spinal deformity she was subjected to x-ray examination. The lower left edge of the 12th thoracic vertebra showed a mere suggestion of osteophyte formation; apart from this there was no sign whatever of spondilitis deformans. At the level of the 11th and 12th ribs on the left side was noted a sharply defined roundish shadow, the size of a grapefruit; its outline was very distinct, and on this account it was assumed to contain some calcified material. On the right side, at the same level, was a similar shadow, but only as large as a mandarin. On x-ray plates taken from the side it was found that these spherical bodies were located towards the back, being apparently retroperitoneal. To clear up the relation between these bodies and the intestines, infusion was given and it was found that the transverse and descending colon was situated above and anterior to the larger shadow. To settle whether similar formations were present in other parts of the body the chest was examined carefully by roentgenography, but no abnormalities were revealed.

It was difficult to say what these shadows might represent, but it seemed most likely that they might be produced by cystic formations of retroperitoneal location. Naturally, the possibility of echinococcus cysts extending from the liver was taken into consideration, and it could not be ruled out entirely, even though it looked as if the shadows of these two bodies were separated from the liver shadow. The possibility of pancreatic cysts was also to be considered, but such cysts might really be expected to be located at a lower level.

X-ray plates of the skull showed no abnormality.

Echinococcus test on the blood gave a negative W. R. —.

On April 11, the patient was transferred to the surgical department; on May 13, she was readmitted to Department D. From the case record of Department A (surgical department) the following data are abstracted:

April 24. *Operation:* Removal of the tumor above the upper pole of the left kidney. The tumor had the size of a large grapefruit.

Microscopic examination: The wall of the cystic tumor was made up of connective tissue. The content of the cyst was a heterogenous mass, whitish in color, somewhat gritty; this material took the stain intensely, and the grits were found to be lime granules, partly of lamellated, concentric structure. In the periphery of this mass were zones or patches of adrenal cortex—or, perhaps more correctly, tissue of benign cortical hypernephroma. No sign of inflammation or malignant neoplasm was evident.

The patient then became able to void normally. She had been somewhat depressed in the surgical department, but she attributed this condition of depression chiefly to the disquietude in the surgical department; she was feeling considerably better after she was moved to a two-bed room in the surgical department. She had not been able to sleep without hypnotics.

The patient noticed that the thyroid enlargement and the pains in the neck subsided somewhat after the operation. She complained, however, of having great difficulties in walking; and particularly of her left leg troubling her; she had pains in both legs, especially in the calves.

The patient looked rather well, but a little suggestive of depression.

The thyroid enlargement was still distinct on palpation, but now the neck/wrist circumferences were only 38/17 cm.

May 15, she complained of pains in the left knee and leg, with impaired sensibility of the left leg; she thought herself that the muscular power of this extremity was lowered. Still, physical examination failed to reveal any abnormality apart from a mere suggestion of foot clonus.

The blood pressure was 140/80 (later, 120/85).

During the remainder of her stay in the hospital she continued to have brief attacks of depression, and her complaints varied, including also lumbago of similar character as prior to the operation. She was in a fair condition of health when discharged on August 1, 1931.

After-examination, November 24, 1931: The patient was still very tired, and at times not able to get up; her spirits were "up and down."

She was still somewhat bloated but there was no longer vomiting; she was severely constipated. No more paraesthesia or twitchings were present. The Chvostek sign was strongly positive.

Examination disclosed no pigmentation except in slight degree of the skin around the eyes and mouth and marked pigmentation around the anus. Her hair was turning grey. The thyroid gland could not be made out on palpation. The neck/wrist ratio was 38/17.5 cm. The weight was 92 kgm. No neurological symptoms could be elicited. The hyperaesthesia of the left leg had subsided completely. The blood pressure was 120 mm.

SUMMARY

This, then, is the case of a 40-year-old single woman who has been feeling unwell for about eight years, and whose condition is most likely to be characterized as pluriglandular dysfunction, the thyroid and the parathyroid being taken as the main factors in her condition, rather than the adrenals. X-ray examination suggested by complaints of pains over the loins and made because of a suspicion of spondilitis deformans revealed the presence of two cysts in the lumbar region. The diagnosis was discussed with the chief surgeon, Dr. Winther, who thought at once that these cysts were probably of the adrenals (perhaps of parasitic nature).

The localization of the cysts was confirmed at operation, and naturally only one of them was removed. The diagnosis was confirmed also on microscopic examination, although the nature of the cysts could not be made out definitely.

It is not unusual that tumors and cysts of the adrenals fail to manifest their presence by special endocrine symptoms (blood pressure, pigmentation, dystrophies) and behave like some other abdominal tumors, giving discomfort merely by their physical pressure upon other structures.

Up to the present, such cysts have been demonstrated only as accidental autopsy findings or under the performance of some abdominal operation; and as far as the writer knows, they have never been diagnosed before by x-ray examination.

WATER OR FAT?

WATER RETENTION IN SO-CALLED ENDOCRINE OBESITY

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A short time ago, two young women presented themselves simultaneously at The Mayo Clinic with essentially the same clinical, diagnostic, and therapeutic problems. They were both regarded as having uncontrollable obesity of endocrine origin. So much that is fanciful or misleading has been written in the field of endocrinology that we present reports of these cases and our ideas concerning them with considerable hesitation. The facts are clearly given in the clinical records. Inasmuch as the treatment in these cases exercised such real control of the condition, the reports are important, even though the hypothesis concerning the condition should eventually prove to be incorrect. In interpreting the data we asked ourselves certain questions and answered them in the form of hypotheses, and on these hypotheses was instituted treatment.

The condition of both patients was regarded as obesity, but the changes in weight have been so rapid that the possibility of retention of water was suggested. The possibility was further emphasized in one case by the actual appearance of intermittent edema and angioneurotic edema, and turgor of the flesh, with the feeling of internal pressure. Actual pitting of tissues at times made the presence of water almost certain. It was thought that secondary hyperactivity of the posterior lobe of the hypophysis, excess of pitressin, or possibly only one of the constituent hormones of the posterior lobe, the water hormone of Kamm, might be present. If true, this gives us a new insight into the nature of the disorder, hyperactivity of the luteinizing hormone of the anterior lobe. This might cause early menstruation and puberty with secondary hyperactivity of the posterior lobe, resulting in retention of water which is often considered pituitary obesity. The latter condition would, therefore, represent an antithesis of diabetes insipidus, that is, hyperactivity of the water hormone of the posterior lobe as opposed to its deficiency in diabetes insipidus.†

With the idea that the increased weight of the patients was in part at least due to retention of water and not wholly to obesity, dehydration pro-

*Read before the 17th Annual meeting of the Association for the Study of Internal Secretions, Milwaukee, Wisconsin, June 12 and 13, 1933.

†Observations made in the Division of Medicine, The Mayo Clinic.

cedures were instituted and followed for a number of weeks, resulting in both instances in striking loss of weight. Mersalyl (salyrgan) was the most effective therapeutic measure in the reduction of weight; ammonium salts were used as an adjuvant.

REPORT OF CASES

Case 1. A woman, aged twenty years, was admitted to The Mayo Clinic, April 6, 1931, with the following complaints: intermittent swellings of the skin of the face, hands, and feet, irregular menses, menorrhagia with painful breasts, leukorrhea, headache, "loss of pep," frigidity and rapid, irregular gain in weight (about 65 pounds). Her parents were alive and well, as were four brothers and four sisters. She had had influenza in 1918. Menses had begun at the age of eleven years, which was earlier than that of her four sisters by two or three years. Bleeding was always profuse, irregular at first, and marked by dysmenorrhea and backache. Her illness began in September, 1929, when she began to lose ambition, and noted urinary frequency and irritability, as well as leukorrhea. She was operated on elsewhere March 17, 1930, when dilatation and curettage revealed hyperplastic endometrium. On abdominal exploration the uterus was found to be of normal size and in good position. The ovaries appeared to be normal. A few cysts of Morgagni were removed from the left fallopian tube; a diseased appendix was likewise removed. Following operation, the urinary symptoms subsided but the leukorrhea continued. Menses occurred every two weeks, and lasted for six or seven days, with profuse flowing. In July, 1930, swellings appeared on the eyelids and lips, and occasionally in the mouth, which made talking and swallowing difficult. These swellings disappeared after twelve to twenty-four hours. Shortly afterward, the hands and feet became affected, and subsequently the skin of the trunk. There was considerable pruritus, and irritation of the skin by scratching would further aggravate the swelling. The condition was not related to foods; the diet was strictly limited for a time without benefit. The symptoms were particularly pronounced during the menses. The patient noted further that for the few days preceding menses and until this period was almost over, the breasts became engorged and tender. The tonsils were removed without relief. The symptoms gradually increased in frequency and severity. Three months before admission the patient became aware of a rapid increase in weight; she would gain 10 to 12 pounds within two or three days. This was especially noticeable if the weather was cold or perspiration slight, and invariably followed a decrease in the output of urine. She could almost predict a gain or loss of weight by measuring the urinary output. In three months her weight increased to 198 pounds; normally she weighed from 135 to 140 pounds. During the eight or nine months preceding admission there was some complaint of frontal headache, not sufficient to incapacitate her. She had gradually become frigid in her reactions toward men.

At the time of examination the breasts were large and pendulous and there was considerable fat over the hips. The body hair was slightly increased. The hair on the head was luxuriant. The hands and feet were red, slightly swollen, and tender; there was slight pitting edema of the ankles and feet, and scattered over the trunk were a few urticarial wheals. Dermographia was slight. The ocular fundi were normal. The blood pressure was 136 systolic and 80 diastolic in millimeters of mercury. A blowing systolic murmur was heard over the heart. The thorax and abdomen were normal, and the uterus was normal in size and position. The thyroid gland was normal. The output of urine was 300 to 1,400 cc. a day; the specific gravity was 1.006 to 1.029. The concentration of hemoglobin was 70 per cent. Erythrocytes numbered 4,380,000. The percentages of the various types of leukocytes were as follows: lymphocytes 37 to 45, neutrophils 59 to 53, and eosinophils 0.5. The concentration of urea was 36 mg., the value for chlorides 635 mg. in each 100 cc. of blood, and the carbon dioxide combining power was 39, 41 and 50 volumes per cent on three different occasions. The teeth were in good condition. The basal metabolic rates were

*This paper was submitted to Doctor John F. Fulton of the Department of Physiology of Yale University, in order to ascertain his point of view concerning the possible relationship of this syndrome to the hypothalamic-vegetative-endocrine complex. He expressed the opinion that irrespective of what the endocrine factor is it is probably secondary to pathologic changes in the hypothalamus and raises the question of "unantagonized parasympathetic innervation to the kidney" as responsible for the disturbance of kidney function. He also refers to the fact that he and Dr. Bailey had reported angioneurotic edema associated with lesions of the third ventricle.

—18 and —19 per cent; the value for serum bilirubin was normal. There was no evidence of tuberculosis in the urine or sputum. Roentgenograms of the thorax, kidneys, ureters and bladder were normal. The stereoscopic examination of the head was normal. A tentative diagnosis was made of urticaria and angioneurotic edema, and obesity of endocrine origin.

Thorough investigation was made of possible leads in regard to the urticaria and angioneurotic edema. There seemed to be no definite relationship to food. Cutaneous scratch tests were made but results were negative, as is so often the case. It was noted that there was a parallel relationship between the fluid balance, that is, the intake of water, the sweating and output of urine, and the swellings. The more fluid was eliminated, the less prominent were the swellings. Diet was not restricted except for limitation of calories to about 1,000 because of the obesity. Marked fluctuations in weight occurred until the fluids were limited, and diuresis and elimination were encouraged by various methods including pilocarpine sweats, purging, and the systematic use of ammonium salts and injections of mersalyl intravenously. Under this program there was a steady loss of weight by loss of fluids. The swellings of the skin were noticeably improved.

Date	Mersalyl cc.	Fluid intake, cc.	Fluid output, cc.	Weight, pounds
5-18-31	0.5			
5-19-31	2	1,200	2,450	165¼ to 164
5-22-31	2	900	2,450	163¼ to 160¾
5-25-31	2	700	2,200	161¼ to 159
5-28-31	2	730	2,300	157½ to 155¼
6-12-31	2	601	2,400	156½ to 155¼
6-15-31	2	600	2,400	151¼ to 150¼
6-18-31	2	750	2,500	152¼ to 149¾
6-22-31	2	680	2,800	152¼ to 148¼
6-27-31	2	600	3,025	150¼ to 144¼
7-11-31		400	2,500	145

It was found that weight could be controlled to a fair degree of accuracy by regulation of the fluid balance alone. After a period of six weeks, the weight was 144 pounds, varying from ½ to 2 pounds a day. Urticaria appeared occasionally. The profuse menorrhagia was slightly decreased; the pain in the breasts continued. The patient was dismissed on trial to determine the efficacy of the program of dehydration. Treatment of the pituitary gland by roentgen rays was considered.

The patient's progress was not satisfactory after her return home. It was difficult, apparently, for her to maintain a strict schedule of fluid balance and, although the drugs were used to some extent, the weight returned to 190 pounds by November, 1931, four months after her dismissal. Further treatment was carried out at home by means of selected foods, control of fluids, and the administration of diuretics, and the weight was reduced to 150 pounds within three months. Apparently the patient is quite comfortable at this level; she has no untoward symptoms of urticaria and angioneurotic edema.

Case 2. A woman, aged twenty-one years, came to the clinic May 23, 1931, complaining of swelling of the abdomen, breasts, neck and thighs, and pain in the right side of the abdomen. She had started menstruating at the age of ten years, three or four years earlier than her sisters. At the age of twelve years she was much more developed than is usual, with a large trunk and white linea alba over the thighs, hips, and breasts. At the age of thirteen years, she began to have pains in the right lower quadrant of the abdomen and constant throbbing, with headaches, and sharp shooting pains in the left lower quadrant and lumbar region, associated with nausea and vomiting, but without diarrhea. Appendectomy was performed in 1914, followed by temporary improvement; however, the swelling continued and transitory enlarged nodes appeared under the arms, and masses appeared in the breast and abdomen. The abdomen swelled greatly at times, but the swelling would subside often in two to three hours; the variation in the circumference of the hips and abdomen at these times was 30 cm. The tonsils were removed in 1929. Subsequent to October, 1930, the swelling had persisted, and for a period of three weeks she had been unable to keep even fluids on her stomach. She gained excessively in weight, 30 pounds in three months. The use of an abdominal belt seemed to afford considerable relief.

The patient was very stout, her hair was luxuriant, her torso massive, the upper part of arms, thighs and buttocks were large, but legs, feet and hands were small (Fig. 1). The thyroid gland was palpable, without nodules. Posterior cervical adenitis was present. The breasts were pendulous but without masses. The lungs and heart appeared to be in good condition. There was slight tenderness in the abdomen, and the right lower quadrant appeared to be somewhat fuller than the left.

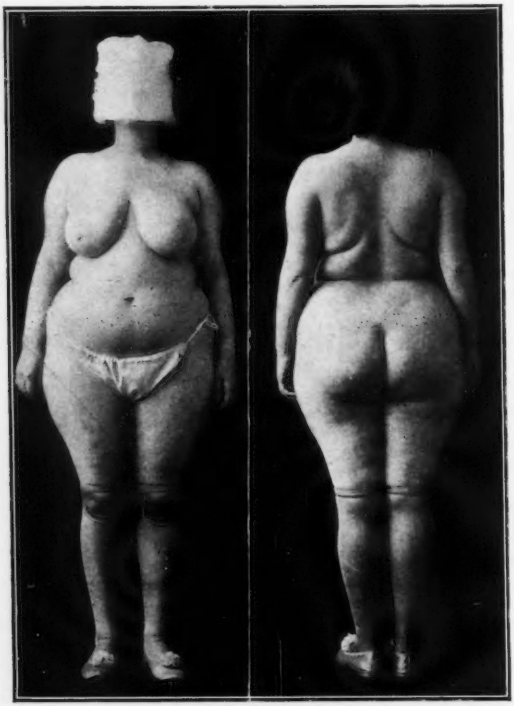

Figure 1 (Case 2). Distribution of deposits of fat or water.

The form of obesity, the marked abdominal distress in the right lumbar quadrant, and the suddeness of the disappearance of the supposed tumor were peculiar. An exploratory operation was seriously considered by the surgeons. The obesity was thought to be of pituitary ovarian type, and the early appearance of the menses suggested an excess of the luteinizing hormone of the pituitary gland. The obesity and lack of stature indicated the possibility of deficiency of the growth hormone of the anterior lobe of the pituitary gland but on further thought, it appeared that the excessive gain in weight might represent retention of water through the presence of an excess of pitressin. Treatment was carried out in accordance with this idea.

The patient was seen in crisis with the abdomen markedly protruding and greatly swollen. When she was asked to stand and contract the muscles of the thigh to the utmost, all her effort was put into this, but while she was in this posture the abdominal tumor disappeared completely. Her attention was called to this disappearance and we explained to her that this was a phantom tumor due to subconscious intra-abdominal pressure; subsequent to this demonstration, it played no further part in her symptoms.

The laboratory findings were normal except for occasional traces of albumin in the urine. Roentgenograms of the skull and thorax showed no abnomalities.

The concentration of urea was 22 mg. in each 100 cc. of blood and the value for calcium was 9.6 in each 100 cc. of serum. The basal metabolic rate was +3 per cent.

With the idea that the water hormone of the pituitary gland was present in excess, a dehydration regimen with ammonium salts and mersalyl was undertaken. The effect on weight and urinary output was as follows:

Date	Mersalyl cc.	Fluid intake, cc.	Fluid output, cc.	Weight, pounds Before Treatment	After
6-2-31	0.5	803	1,000	159½	158½
6-3-31	1.5	800	2,100	157	151 to 148 to 147½
6-20-31	1.0	400	1,400	151	150
6-23-31	1.0	600	1,900	148	145
6-27-31	1.0	600	1,200	147½	146
6-29-31	1.5	500	1,800	143¾	136½

The reduction in weight was not accomplished without marked and rather disturbing reaction. The injection of 1.5 cc. of mersalyl caused severe nausea. Vomiting persisted for several days; it became so extreme that 600 cc. of 10 per cent glucose was given intravenously with sedative doses of chloral hydrate. The patient lost 11 pounds in four days but the reaction was rather alarming. After a period of two weeks had elapsed smaller doses were employed. Ammonium salts at first were poorly tolerated but later, ammonium nitrate in doses of 2 gm. three times a day was taken without undue difficulty. These subsequent doses of mersalyl were given for a week but with a return to the use of 1.5 cc. the marked nausea and vomiting returned and were stopped after four days only by the administration of 10 per cent glucose and 1 per cent salt and chloride, by mouth and rectum. During this period albumin, graded 1 to 2, appeared in the urine and the concentration of urea increased to 58 mg. in each 100 cc. of blood in the first episode, and to 44 mg. in the second. However, no emergency resulted.

The patient left the clinic June 30, 1931. She had lost 22½ pounds and the size of the body was remarkably decreased. She was sent home and a diet low in calories was advised. Water was restricted to 800 to 1,200 cc. a day, ammonium nitrate in doses of 4 to 6 gm. daily was given, and the use of an abdominal belt was recommended. On this regimen she did fairly well until February, 1932, when she wrote saying that her weight had increased 13 pounds in the preceding few weeks. Further, mersalyl, in doses not to exceed 1 cc. at a single injection and small doses of thyroid were advised. The weight, March 1, 1933, was 130 pounds. The patient expected to be married at an early date.

COMMENT

Striking reduction of weight was accomplished in both cases through the restriction of calories and liquids, together with dehydrating agents. Injections of mersalyl constituted the most effective measure since continuation of the other procedures failed to hold the weight when the mersalyl was discontinued. In both cases mersalyl will have to be used again if reduction in weight is to be maintained. The effect on angioneurotic edema should be mentioned incidentally, as there was no question in the minds of observers as to the decrease in the severity of the manifestation during the period of dehydration. It was not, however, fully controlled at any time during the course of treatment. The relationship between the angioneurotic edema and retention of water, as such, offers interesting matter for speculation. So far as we know, the example presented here is unique. Deductions in regard to the factors causative of the angioneurotic edema are not justified except that in this particular instance it is associated with a syndrome of endocrine imbalance.

The pituitary basis for this retention of water has not been proved, either pathologically or by changes in the sella turcica observed roentgenologically; it is simply a matter of inference. This inference is strengthened somewhat by the fact that both patients had severe headache during the period of increased weight. In the event that difficulty is experienced in duplicating the results the patients obtained through dehydration, a further procedure would seem indicated, namely, irradiation of the pituitary glands by means of deep roentgen rays or radium. This has been discussed with both patients and will probably be tried if the need becomes marked.

SUMMARY

The cases are described of two women, 20 years of age, who were sent to The Mayo Clinic with what was considered endocrine obesity of rapid onset. Menstruation and puberty in both instances took onset three or four years prematurely, followed by rapid, inexplicable and marked obesity developing between the ages of 18 to 20 which resisted all forms of antiobesity management. On physical examination both patients were seen to be superlatively feminine in appearance with luxuriant hair and exaggerated feminine configuration. One patient had menstruated at two-week intervals and presented also urticarial lesions and angioneurotic edema. Proceeding on the basis of deranged water metabolism, these patients were subjected to dehydration through the use of ammonium salts and the newer mercurial compounds with reduction of weight to practically normal. On returning home the weight was regained in one patient but in the other fully controlled through the use of ammonium and mercurial compounds and water restriction. It was thought that this syndrome might be explained on the basis of an early excess of Prolan A resulting in early puberty and a subsequent excess of pitressin resulting in water retention. The syndrome may be regarded as the antithesis of diabetes insipidus.

IS SPORADIC GOITER DEPENDENT UPON GENOTYPICAL FACTORS?

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A married woman, aged 46 (genealogical register Fig. 1, No. 6), was admitted to this department under the diagnosis hyperthyroidism. On examination her eyes were found to be a little moist and rather staring; there was a rather large swelling of the thyroid, involving every part of the gland but most pronounced over the left lobe and the left part of the isthmus; on palpation, this goiter did not seem altogether uniform, but rather nodular, and in the isthmus there was a palpable nodule the size of

Fig. 1

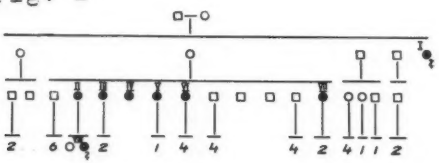

Fig. 2

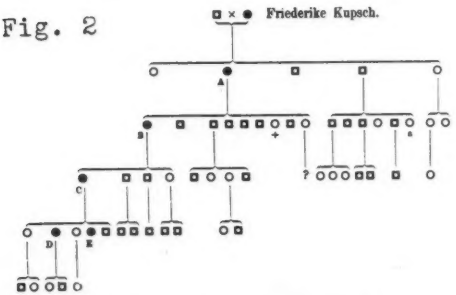

Figure 1. Genealogical chart showing incidence of goiter in family reported.
Figure 2. Genealogical chart of Siemen's cases.

a walnut. The skin was moist from sweating; the vasomotor skin reflexes were exaggerated. There was a distinct and typical Basedowian tremor of the hands. Tachycardia was present, with a pulse rate of about 120 that was liable to rise considerably on emotional stimulation. Her basal metabolism was determined as being 151 per cent; two days later it was 143 per cent.

On thorough inquiry into the past and family history of the patient, two facts were revealed. She stated that she had had her goiter since she was 21, and that it had now been present for 25 years without giving her

any local or general symptoms, until about half a year before, when general symptoms began to appear in the form of nervousness, anxiety, shaking, palpitation of the heart, and loss of weight—symptoms which she claimed were brought about by a personal grief. She further stated that she had five sisters, all of whom had goiter, and also that an aunt and a niece had undoubtedly been afflicted with goiter. These data have prompted me to further examination of the family. A survey of its various members may be seen in a genealogical record (Fig. 1).

The group of children to which this patient belongs was comprised of five brothers and six sisters. One brother died in infancy, while four are living; I have examined them, and none of them has goiter. One sister (Fig. 1, No. 5) died in puerperium at the age of 22. Her sisters state that, like the rest of them, she had a "thick neck." I have examined the other five, and all of them have goiter. Details of these examinations are given below.

The mother of these children died at the age of 86 years. All the children agree that her neck was thin and slender, without any suggestion of a goiter. The mother had two sisters and two brothers; and one of her sisters (Fig. 1, No. 1) is said to have had a "thick neck." But, according to the statements of the family, the other three members of that generation and their descendants have been entirely free from goiter.

The father died when he was 68 years old; he is also said to have been free from goiter. He had had one sister who died at the age of 6, and five brothers without any evidence of goiter—as far as the obtainable data of the family history go. The five brothers of the father have altogether 30 children, who are all said to be free from goiter. It is of no use to go further back in the family history, as the obtainable data on the former generations are not reliable; at any rate, nothing is known of the presence of goiter in the grandparents or in the more remote ancestors.

In turning to the last generation, as illustrated in Fig. 1, we find a group of children, with boys and girls almost equal in number, the oldest being 25, and the youngest 5 years of age. In this generation one girl (Fig. 1, No. 8) died of erysipelas at the age of 21. Her relatives think that her neck was "a little thick," but the information on this is very uncertain. Apart from this case there has not been any evidence of goiter in this generation—and most of its members have been examined personally.

So in this family we have six sisters with goiter and one maternal aunt, who is said to have had a goiter, besides a daughter with a questionable goiter. The principal data, with a view to the goiter in these eight cases are as follows:

Case I. A. J., single; died at the age of 64. She is said to have been "small and stunted in growth." Her face was broad, her back was broad, and she had a "peculiar thick neck." Mentally she was very far behind in development, and she had never gone to school, as she would have been unable to keep up with the teaching. "Later she was able to knit a little," but her mental faculties did not reach beyond this accomplishment.

Case II. J. T., married, 53 years old. Seven years ago she noticed her goiter for the first time. It made its appearance after a bicycle trip she took with a sister (case IV). During these past seven years the goiter has been progressing to some extent, but it has not caused her any discomfort. During the last half year she has had some palpitation of the heart, and has been losing weight, but this she attributes to her grief at the death of her daughter about that time.

The examination showed a goiter localized chiefly to the isthmus where a roundish nodular body, about the size of a walnut, was distinctly palpable; in addition there was a moderate enlargement of both lobes of the thyroid. The smallest circumference of the neck was 33 cm., the widest 38 cm. There were absolutely no eye symptoms of exophthalmic goiter, no exaggeration of the vasomotor reflexes. There was a little tremor of the hands and a slight tachycardia during the examination; but on a subsequent examination, when the patient felt more at ease, it is questionable whether there was really any pathological tremor of the hands. The pulse rate was only about 80, the basal metabolism was 115 per cent and her weight (with clothes on) was 59 kg.

Case III. S. J., married, 51 years old. About 21 years ago she noticed her goiter the first time. Since then it has been progressing but slightly. There have never been any local or general symptoms. For a while she was under treatment with iodine, and this is said to have reduced the circumference of her neck by 4 cm.

There is now a goiter chiefly localized to the isthmus, where there is a roundish protrusion, rather well-defined, about the size of a hen's egg; there is a moderate enlargement of both the lobes of the thyroid. The smallest circumference of the neck is 39 cm., the widest 43 cm.

There are no eye symptoms of exophthalmic goiter, and no exaggeration of the vasomotor reflexes. During the examination there was a little tremor and tachycardia, but these phenomena subsided rapidly. At the end of the examination the pulse rate was 100 and the weight was 101 kg.

From February 27 to March 29, 1930, the patient was under treatment in the Med. Dept. A of the Rigshospital, under the diagnosis: Angio-neurotic oedema (Quincke's disease); Goiter; Adipositas. Her weight was 90.5 kgm. the basal metabolism was 104 and 105 per cent, and the pulse 66 to 72. X-ray plates showed a slight compression of the trachea, the pressure being exerted from both sides.

Case IV. E. F., single, aged 50. She noticed her goiter the first time about seven years ago, following a bicycle trip she made with a sister (Case II). Since then the goiter has been progressing gradually. It has given neither local nor general symptoms.

The examination showed a goiter of moderate size, most pronounced over the right lobe, where a roundish node—the size of a walnut—was distinctly palpable. The smallest circumference of the neck was 32 cm., the widest 35 cm. There were absolutely no eye symptoms of exophthalmic goiter, and no exaggeration of the vasomotor reflexes. There was an unquestionable typical tremor of the hands, and this was said to have been noticeable the last two years. There was tachycardia at the very beginning of the examination, but 15 minutes later the pulse rate was 92. (The patient stated that her pulse rate was usually about 90.) Weight (with her clothes on) was 66 kg. The basal metabolism was 105 and 106 per cent.

Case V. J. H., married, died in puerperium at the age of 22. As already mentioned, she is said to have had a "thick neck," like the other sisters, but I am unable to obtain any detailed information as to the duration of her goiter and the size it attained.

Case VI. G. M., married, 46 years old. This is the patient who was admitted to this hospital and whose case is mentioned in the introduction of this paper.

She noticed her goiter the first time about 25 years ago, after her first parturition. Since then, the goiter has been progressing gradually, particularly in connection with the three subsequent parturitions. There have been no local or general symptoms until half a year ago, when there began to be noticeable, nervousness, anxiety, tremor, tachycardia, and loss of weight.

The examination showed a goiter of moderate size, most pronounced over the left lobe and the isthmus. Over the isthmus the surface appeared to be somewhat nodular, and on palpation one could distinctly make out a well-defined nodule, the size of a walnut. The smallest circumference of the neck was 34 cm., the greatest 39 cm. The expression of her face was slightly staring, and the eyes

were a little moist; there was some exaggeration of the vasomotor reflexes; there was a distinct and typical tremor of the hands. On the first examination the pulse rate was 144; later it was about 120. Her weight (nude) was 68 kg. The basal metabolism was 151 and 143 per cent.

Case VII. P. P., married, aged 36. She noticed her goiter 13 years ago and it has been progressing gradually. There have been periods with palpitations of the heart.

The examination showed a diffuse goiter of moderate size, most conspicuous over the isthmus. There were no eye symptoms of exophthalmic goiter, and no exaggeration of the vasomotor reflexes; there was only slight tremor of the hands. The pulse rate at the examination was 100. Her weight with clothes was 82.5 kg.

From July 18 to August 17, 1931, she stayed in the Med. Dept. of Copenhagen County Hospital, where the physical examination showed constipation, several nervous symptoms, and a diffuse enlargement of the thyroid. There were no eye symptoms of exophthalmic goiter, and only a little tremor of the hands. The pulse rate was 80, and the basal metabolism was 106 per cent.

Case VIII. E. J., single, died of erysipelas at the age of 21. Like the other above-mentioned members of her family, she had also a "thick neck," but no particular attention was paid to this abnormality. Now it is impossible to obtain any reliable details as to the size of the goiter in this case.

Table 1 gives the present age of these patients in whom the duration of the goiter is known, together with the values of the basal metabolism in the respective cases.

TABLE 1

Name	Present Age	Persistence of Goiter	Basal Metabolism	
J. T.	53	7 years	115%	115%
S. J.	51	21 years	104%	105%
E. F.	50	7 years	105%	106%
G. M.	46	25 years	151%	145%
P. P.	36	13 years	106%	

How are we now to classify the goiter cases encountered in this family? It is a well-known fact that exophthalmic goiter appears not infrequently as a hereditary condition. But the cases herein described are decidedly different from the ordinary clinical picture of exophthalmic goiter. In these cases the surface of the goiter is more or less nodular, without the diffuse character usually found in exophthalmic goiter. Furthermore, the goiter has persisted a great number of years—up to 25—without being accompanied by the ordinary symptoms of hyperthyroidism. Only one of these patients showed very late—after the goiter had persisted nearly 25 years—symptoms of hyperthyroidism: nervousness, restlessness, loss of weight, tremor, tachycardia, and increase of the basal metabolism. In this case the simple goiter finally assumed some of the characteristics of exophthalmic goiter; and it seems perfectly justifiable to claim that this is not a question of hereditary occurrence of the ordinary exophthalmic goiter.

Endemic goiter accompanied by cretinism has been observed in Denmark only once, by Christensen. In six children belonging to three different, non-related families who had been living in two houses at the edge of the same swamp in the southern part of Seeland, there developed cretinism with or without goiter, quite identical with the cretinism and endemic goiter encountered in certain mountainous districts. But in the case of the family here presented, there is no reason whatever to assume that

the goiter of these sisters falls under the heading endemic goiter. It is quite true that all six sisters grew up in Copenhagen, but at the time when their goiter was first noticed—evidently in its earliest development—they had been separated a long time, living in different parts of Copenhagen and its suburbs. Their maternal aunt, who according to their statements had also had a goiter, had lived all her life in an entirely different part of Seeland. Though it must be admitted that goiter may be present for a considerable length of time without being noticed, here it is still warrantable, I think, to rule out the improbable possibility that these cases may be instances of endemic goiter in the ordinary sense of this term.

There remains, then, sporadic goiter, cases of which are encountered in Denmark now and then, apparently isolated. By the more or less nodular character of the goiter, by its long duration, and by its infrequency of complications with symptoms of hyperthyroidism, the cases here described of hereditary goiter resemble the ordinary sporadic goiter.

OBSERVATIONS FROM THE LITERARURE

The literature mentions two families with a similar incidence of goiter. One is reported by Siemens, in 1917 (Fig. 2), with six cases of goiter in five successive generations. The other is reported by Bluhm, in 1921 (Fig. 4), comprising 15 cases of goiter. But, in some cases of the latter group,

Fig. 3

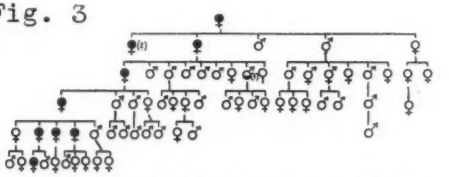

Abb. 1. Erblicher sporadischer Kropf. (Eigene Beobachtung.)

Fig. 4

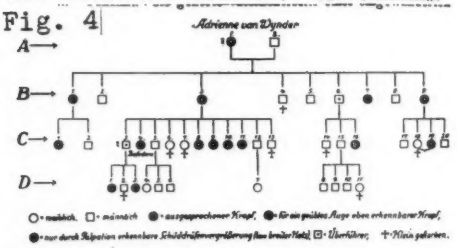

Figure 3. Siemen's findings, reviewed.
Figure 4. Genealogical chart of Bluhm's cases.

the diagnosis appears to have been open to doubt, being made on a "nur durch Palpation erkennbare Schilddrüsenvergrösserung." These two families had been living in districts where endemic goiter was not encountered, and the various goitrous individuals had been separated by space and time.

Clinically, the cases in the families reported by Siemens and by Bluhm and in the family reported here appear to be identical. In all of the three genealogical records the presence of a goiter has been established only in women. Taken altogether these three genealogical records give a total of 28 women with goiter, and not one man. Even though the diagnosis may be questionable in some of these 28 women, the sex difference is no less conspicuous. This limitation to the female sex does not appear to be absolute, however. In 1924, Siemens gives a somewhat more detailed account of his aforementioned family (see Fig. 3). Now the record covers six generations, giving nine cases of goiter in women and one case of goiter in a man. But Siemens himself thinks that the last case (in a man) is very doubtful. In addition, Siemens mentions that a fellow physician had told him of another family of this kind, in which goiter was said to be present in a few of the male individuals, too. Details concerning this last family are lacking, however. In discussing this question, in 1925, Siemens further mentions that Bluhm told him she had later had an opportunity of observing a new family with instances of sporadic goiter in three generations, including a pronounced case of goiter in a man. In a family to which my attention has been called recently, though I have not as yet had an opportunity to examine it in detail, I have ascertained so far the presence of goiter in two women and one man. For the sake of comparison, it may be mentioned that, amongst others, Kocher states that in typical exophthalmic goiter the proportion is nine women to one man; in typical and atypical cases of hyperthyroidism considered together the proportion is six to one; in endemic goiter the proportion is about five to one; and in sporadic goiter it is also five to one. Möller, 1925, mentions 35 patients with sporadic goiter—33 women and two men. If this proportion is representative of conditions in general, it follows that in most instances where the hereditary character of the goiter seems evident, only the female sex will be represented by the patients.

In all the three families discussed above the goiter seems to have made its appearance—or, at least, to have been noticed—in fairly near the same age-class. In Siemens' family the age was from about 20 to 35 years; Bluhm does not give the exact age of the goitrous individuals in her family, but they seem to fall in about the same age-class; and in the family I have observed, the age of the goitrous individuals at the time the goiter was first noticed has been from about 20 to 46 years.

In all these three families, as a rule, the goiter has been more or less nodular; in most instances the right lobe of the thyroid has been larger than the left; in some of the cases the goiter has been very large, up to the size of a child's head; and in a few of the cases the goiter has given pressure symptoms, necessitating thyroidectomy. In one of these cases (Bluhm) symptoms of hyperthyroidism supervened at the age of 61. Hypothyroidism seems to have been present in No. 1 of the family I have reported.

COMMENTS

The accumulative occurrence of goiter in these families indicate most forcibly that the disease is entirely or partly dependent upon genotypical factors. There has been no demonstrable influence of external conditions upon the development of the disease.

As to a more precise characterization of the genotypical basis of this disease, for the present one may venture to express himself on this question only with reservation. From the occurrence of the goiter in the two genealogical records reported by himself and by Bluhm, Siemens assumes that the disposition to goiter is dominant, but sex-limited to women. In fact, this dominance seems to assert itself very distinctly in the two families concerned—in the family observed by Siemens this property is even inherited directly in as many as six successive generations. Siemens explains the sex-limitation to women as indicating that even if this character is present in the men, it fails to develop and manifest itself, being suppressed by the male characters of the organism.

The family I have reported does not lend any support to the assumption of the dominance of this character. The mother of the six sisters is said to have had no enlargement of the thyroid whatever, and yet she is presumably to be looked upon as the connecting link in the hereditary chain—that is, if it is correct that one of her sisters had goiter. But this may be disputed, however (see above). Still, phenotypical good health of the mother of the six sisters by no means precludes the possibility that she might have been a carrier of the goiter character, for dominance is often a rather relative quality, especially in properties that do not manifest themselves till comparatively late in life (incomplete dominance). Nor does the phenotypical good health of the father of the six sisters preclude that the goiter character might have come from him. But, as already mentioned, goiter has never been noticed in any of his relatives.

It is more difficult to explain why every one of the six sisters presents this property. Leaving out the far-fetched possibility that by chance the ball may land on black six times in succession, skipping white altogether, it is almost a conclusive supposition that the mother must have been homozygous, or that the character must have been latent in the father as well as in the mother.

It has been mentioned already that the sex-limitation* cannot be taken to be absolute, and, therefore, it seems natural to consider it analogous with the liability of women to other thyroid affections. It is a well-known fact, illustrated by a few statistical figures above, that hyperthyroidism as

*Sex-limitation is not to be mistaken for sex-linkage. In the first instance the character is resting with one of the ordinary chromosomes, but its development is limited to one sex, because the development of the special characters in the other sex inhibits the development of the first mentioned character. So the sex-limitation is only indirectly of genotypical nature. Sex-linkage is something different. Here the character in question is resting with the X-chromosome, and its inheritance and possibility of development are linked with the presence of two X-chromosomes in women and one X in men. Sex-linkage does not mean that the character is limited to one or the other sex; it means only that the character is carried by sex-chromosomes.

well as endemic goiter and sporadic goiter are far more frequent in women than in men. That this sex-difference in the occurrence of goiter is chiefly dependent upon the development of the secondary sex characters, the male features of the organism, seems evident, for one thing, from the fact that Dieterle, Hirschfeld and Klinger found the endemic goiter to be almost equally frequent in the two sexes before puberty. After puberty the frequency of endemic goiter fell off in both sexes, but most in the male. A somewhat similar sex-difference does evidently apply to exophthalmic goiter, too, that is, if Siegert is right when he states that the proportion between male and female patients with this disease is 1:3 in children, and 1:9 in adults.

Whether the genotypical basis of sporadic goiter is specific for this disease, or whether it is common to several diseases of the thyroid, is a question calling for further investigation. As mentioned before, exophthalmic goiter is not infrequently hereditary in its occurrence, usually in this way, that several female members of the family are—or have been—suffering from this disease. Yet I would be inclined to think that in this disease the genotypical basis is specific and differing in nature from that of sporadic goiter.

In the case of endemic goiter it is doubtful whether any special genotypical basis is underlying this condition. In an uncritical period this has been answered in the affirmative; and Riebold, who has studied this problem, has given a number of genealogical records in order to demonstrate the hereditary occurrence of this disease. His evidence has rightly met with severe criticism, and the method can be designated only as unfit for use in districts where endemic goiter is very prevalent, and where the various members of the families examined have been exposed to the special outer conditions bringing about the endemic occurrence of the goiter. Later the question of hereditary factors in the occurrence of endemic goiter has been taken up for study in identical twins (Siemens, Weitz); it has been found that in goitrous districts identical twins (one ovum) would both show a goiter appearing at the same time and developing to the same degree, whereas distinct twins (two ova) were liable to considerable variations in this respect. In my opinion, however, these findings do not show anything particular beyond the fact that identical twins react in a practically identical manner to presumably somewhat identical outer agencies; and I cannot look upon these findings as supporting the assumption that there must have been a specific genotypical basis for the development of this disease.

But, for the present it would seem that the most interesting question associated with the hereditary appearance of sporadic goiter here reported is not the details in the character of the genotypical basis of these cases but, on the contrary, the question, whether the apparently isolated instances of sporadic goiter which are encountered not infrequently, may not actually be of quite the same nature as the aforementioned hereditary

cases—i.e., dependent upon the same genotypical factors. And I take this possibility to be the most probable. In the first place, I think, one can by no means be sure that these sporadic cases are so isolated in their occurrence as they appear to be. It is quite a common fundamental rule, established again and again in many diseases of genotypical origin, that the hereditary factor has been recognized only on meeting with families in which some accidental conditions have made this factor the more conspicuous. Then these families have been reported, giving rise to a discussion of the hereditary occurrence of the disease in question, and by and by it has become evident that there is a gradual transition from such families to other families in which the disease concerned has made its appearance as an apparently isolated instance; and then it has been realized that it is impracticable to make any sharp distinction between the two groups of cases. In this connection, it suffices to mention such diseases as diabetes mellitus and pernicious anemia, the accumulative occurrence of which in certain families has shown that the development of these diseases is dependent upon genotypical factors; and now there is hardly anybody who will question that the apparently isolated cases of these diseases are, as a rule, dependent upon the same genotypical factors. I am therefore inclined to think that if one would pay close attention to every case of apparently sporadic goiter met with, and if one would inquire very thoroughly or examine personally for the presence of goiter in other members of the family, one might now and then—not infrequently—be able to demonstrate the existence of other cases of this disease in the same family —quite in analogy with the findings from such inquiries into diabetes mellitus and pernicious anaemia.

This view has been corroborated during the past year, after I had commenced to make inquiries about a possible hereditary occurrence of the disease in the families of the goiter patients who have been admitted to this department or whom I have met with elsewhere. During this period I have very often been able to ascertain a hereditary occurrence of sporadic goiter.

So it does not seem improbable that the reported instances of families with hereditary occurrence of sporadic goiter throw some light on the etiological explanation of the apparently isolated instances of sporadic goiter, suggesting very strongly that the latter are also dependent upon genotypical factors.

The pathogenesis of the cases here described, however, is as yet an altogether obscure question. In the case of endemic goiter it is, as is well known, still the prevailing theory that a deficiency of iodine is the cause of the disease—a want of iodine so marked that its effect asserts itself even in the absence of any special disposition to the disease.

In goiter dependent on genotypical factors it does not seem reasonable to assume the coexistence of such an absolute deficiency of iodine. The families mentioned have all been living in districts where an absolute lack

of iodine and endemic goiter are unknown; and the fact that these goitrous individuals have been separated by space and time, makes it inconceivable that an absolute lack of iodine might have asserted itself in the different places and at different times. If one would imagine some connection between the pathogenesis of the disease and a lack of iodine, the latter would, perhaps, rather have to be a relative iodine insufficiency hinging upon an anomaly of the iodine metabolism.

SUMMARY

Report is given of a family observed by the author, with hereditary appearance of sporadic goiter amongst the female members of the family.

A few similar observations have been reported before (Siemens, Bluhm).

The hereditary occurrence of the disease indicates that it is entirely or partly dependent on genotypical factors.

It is rather probable that the apparently isolated instances of sporadic goiter are likewise dependent upon genotypical factors.

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GASTRO-INTESTINAL DISTURBANCES ASSOCIATED WITH THE ENDOCRINOPATHIES

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The gastro-intestinal tract doubtless plays an important rôle in regulating many of the activities of the human organism. The results of certain disturbances of gastro-intestinal motility, especially those associated with obstructive lesions of the stomach or bowel are generally known. Such affections as constipation or diarrhea may likewise frequently have dire effects upon the body, often as a result of vague toxic disturbances as well as other processes not altogether clearly understood. In like manner, disturbances of secretion may give rise to untoward effects, and symptoms such as "indigestion" become manifest, again not only because there is imperfect digestion of food itself but also because the organism in general is affected as a consequence of the absorption of toxic products.

On the other hand, disease processes elsewhere in the body may also produce a marked secondary effect upon the gastro-intestinal tract and even though the stomach and intestine may become involved late in the clinical picture, the digestive symptoms may become so dominant as to overshadow those produced directly by the primary affection.

This interrelationship is in no way more clearly shown than by that existing between the digestive tract and the ductless glands. The study of the relation of endocrine to gastro-intestinal functions has become a matter of increasing interest. Much has already been accomplished in the solution of this difficult problem but much more still remains to be determined.

When the relation of disturbances of the endocrine system to gastro-intestinal disease is considered, the problem becomes even more intricate. As yet the fact has not been definitely established as to whether the gastro-intestinal disturbances so frequently observed in endocrine disease are directly due to the latter affection itself or are secondary to changes in the autonomic nervous system which in turn seem to be the result of the endocrinopathy.

According to the classic studies of Eppinger and Hess (1), the theory was advanced that there existed normally an equal and continuous tonic innervation of the vagus and sympathetic nerves. Under normal conditions these opposing systems are maintained in a state of equilibrium; however, when the tonus of one or the other is increased a corresponding state of vagotonia or sympatheticotonia occurs.

The evidence pointing to the presence of this opposing nerve influence can be easily demonstrated in rabbits in which pylorospasm can be experi-

mentally induced by stimulation of the vagus and inhibited by stimulation of the splanchnics. According to Rogers, the same phenomenon may be brought about even in a more prolonged and graphic manner by subcutaneous injection of certain extracts of the thyroid, parathyroids or pyloric musoca into dogs. He was thus able to produce a marked increase both in the flow of the gastric secretion and in gastric motility which could be inhibited by means of an injection of atropin. Not only will atropin inhibit this reaction but a similar effect can be brought about by the injection of an extract of the adrenal glands. He explains the latter reaction as due to a stimulation of the sympathetic by the extract of this gland. According to Rogers: "If the experimented animal is angered or excited, which is akin to worry in the human being, the gastric juice ceases to flow, due to the inhibitory influences carried to the stomach along the sympathetic. After a prolonged stimulation the sympathetic becomes partially or fully fatigued, allowing the vagus full play, free of inhibition, in consequence of which hyperacidity, hypermotility or pylorospasm is produced, which may be followed, if this condition is much prolonged, even by ulceration." The cause of pylorospasm, therefore, according to Rogers, is a continuation of the original failure of the sympathetic.

As yet, however, the relation of the secretion of the ductless glands and the functions of the vegetative nerves has not been entirely satisfactorily explained. Certain facts have, however, been definitely established as, for example, the influence of the adrenal gland in increasing the tonus of the sympathetic system. On the other hand, when considering the thyroid some maintain that it acts only through the sympathetic, while others suggest that it produces its effect through the vagus, and still others attribute to it both sympathetic and vagotonic actions.

Although a neurogenic influence is recognized to exist among the other endocrine glands no statement can be made as to its positive nature. For instance, while stimulation of the sympathetic is produced by the adrenals, its antagonistic hormone and its vagus stimulator still remain unknown. However, it may be generally maintained that the influence of the endocrines is largely exerted upon the gastro-intestinal organs through the medium of the vegetative nervous system.

According to Bayer and Peter (2), the pituitary gland seems to exert a double action in the paralytically distended bowel. After a preliminary relaxation there is a strong contraction, especially of the rhythmic movements of the intestine. They consider the preliminary phase as due to stimulation of the sympathetic fibers inhibiting the muscles, the second phase as due to stimulation of Auerbach's plexus and of the post ganglionic fibers.

There still remains a third method by means of which the endocrines may exert their effect upon the gastro-intestinal tract, that is by direct action upon the receptive glands. Whether this effect is brought about by

influences upon the intrinsic nerves in the organs affected, or by direct chemical action, cannot as yet be stated.

Therefore, in considering the effect of the endocrines upon the gastro-intestinal organs, three mechanisms must be considered:

(1) Through the stimulation of the control part of the vegetative nervous system.

(2) By stimulation of the post ganglionic fibers and nerve plexuses of the organs themselves.

(3) By direct action of the hormone on the receptive organ.

It is evident that as yet our knowledge regarding the action of the endocrine upon the gastro-intestinal functions is still far from clearly established and that more positive evidence is required before definite conclusions can be arrived at regarding this important subject.

THE DIGESTIVE TRACT IN THYROID DISEASE

The thyroid is among the most important of the ductless glands. Through its internal secretion it influences the physical development of the child and the mental activity of the adult. Among its many functions is its control over the changes in the amino-acids of cell metabolism of the human organism as a result of which oxidation occurs with the production of carbon dioxide, ammonium carbonate and water. Timme (3) has recently again emphasized the fact that the thyroid rarely functions alone and that any disturbance of this gland always induces a change in function of other glands such as parathyroids. Similarly the suprarenal cortex and the anterior lobe of the pituitary may also become secondarily involved. He points out in general that whenever thyroid dysfunction exists, the involvement no longer remains entirely confined to this gland but becomes a multiglandular disturbance. Timme calls attention to the special functions of these coordinating glands in an attempt to explain the varying types of symptoms which are manifested. For example, in some instances the blood pressure is found to be low; in others, high. Some patients are excited or overstimulated while others are depressed.

According to Timme, the patient who is affected with vagotonia should be classified in the same group as a patient who has a suprarenal cortex which is imperfectly balanced by the thyroid. This picture is accompanied by a lowering in blood pressure and a vagus overstimulation rather than an increased sympathetic response.

The thyroid in combination with the other ductless glands therefore plays an important rôle in human economy. It presides over the nitrogenous metabolism and, when it functions abnormally, this process becomes either accelerated or retarded. If its secretion is excessive the body tissues are abnormally stimulated almost to a degree of wasting dissipation and in consequence tachycardia, muscular weakness, loss of weight, tremors, sweating and increased mental activity occur. If the secretion is deficient

the body metabolism is lowered with a diminished heat production. The skin is dry, the hair course and myxedema may follow or the mental development remain infantile.

Thyroid dysfunction plays an important rôle in the production of digestive symptoms both in the secretory and motor spheres. In Tinker's (4) series of 4127 thyroid cases, 1415 or one-third of the total number of patients complained of digestive symptoms of more or less severity. Over 10 per cent of these cases complained of persistent nausea and vomiting and 10 per cent had intense diarrhea. Tinker points out that although the usual medical measures were employed these symptoms were controlled only with great difficulty. In our experience, extending over a series of many thousands of cases of varied digestive disturbances about 15 per cent presented symptoms associated with thyroid dysfunction. Of these about 10 per cent were of the hyperthyroid and about 5 per cent hypothyroid type.

The following table modified from that of Friedenwald (5) presents the vagotonic and sympatheticotonic syndromes associated with the gastro-intestinal tract.

MONOSYMPTOMATIC GASTRIC NEUROSES

Vagotonic Group:
- Cardiospasm
- Pylorospasm
- Peristaltic Unrest
- Pneumatosis
- Nervous Vomiting
- Eructatio Nervosa
- Rumination
- Regurgitation
- Gastralgia
- Hyperesthesia
- Bulimia
- Gastromyxorrhea
- Hyperchlorhydria
- Gastrosuccorrhea

Sympathetictonic Group:
- Atony
- Incontinence of Pylorus
- Acoria
- Anorexia
- Achylia Gastrica
- Hypochlorhydria

MONOSYMPTOMATIC INTESTINAL NEUROSES

Vagotonic Group:
- Intestinal Fermentative Dyspepsia
- Nervous Diarrhea
- Enterospasm
- Spastic Constipation
- Enteralgia
- Hyperesthesia
- Peristaltic Unrest
- Meteorism
- Mucous Colitis
- Spasm of Anal Sphincter

Sympatheticotonic Group:
- Atony
- Atonic Constipation
- Paralytic Ileus
- Relaxed Anal Sphincter

POLYSYMPTOMATIC GASTRO-INTESTINAL NEUROSES

Nervous Dyspepsia.

1. GASTRO-INTESTINAL MANIFESTATIONS INCIDENT TO HYPERTHYROIDISM

The gastro-intestinal symptoms occurring in hyperthyroidism include, according to Barker (6), disturbance of the salivary secretion, of the appetite, of the gastric secretion and motility, of intestinal secretion and of carbohydrate metabolism.

In hyperthyroidism the salivary secretion is usually diminished, producing a dryness of the mouth, though occasionally this secretion is increased. The appetite, ordinarily markedly increased in the early hyperthyroid state, often becomes capricious and is finally diminished to a degree of complete anorexia in the late stages of the affection.

Though some writers state that excessive thyroid activity is associated with increased gastric secretion and hyperchlorhydria, it is generally admitted that this assertion is incorrect. The gastric secretion is usually diminished though occasionally hyperchlorhydria occurs and especially in those instances in which gastric crises supervene. King (7), Lockwood (8), Moll and Scott (9), Moll and Flint (10), Brown (11), Lerman and Means (12), and Moore (13) are all convinced that a lowered acidity with a tendency to an achylia is commonly noted in this condition. Lockwood reports an achlorhydria in 10 cases of a series of 24 of hyperthyroidism and Moore in 37 of a group of 47 (78 per cent). Moll and Scott performed fractional analysis in 50 cases of hyperthyroidism. Of these subjects 22 showed achlorhydria, 15 hypochlorhydria and 13 normal or high normal acidity. The average duration of symptoms in achlorhydric cases was 2.9 years, in hypochlorhydric cases 1.1 years and in cases with normal secretion 0.5 years. This suggests that the diminution of hydrochloric acid secretion occurs in the course of the disease and is not a predisposing cause. Of the cases of achlorhydria 60 per cent were due to duodenal regurgitation. The low acid secretion and the achlorhydria which have been so constant in the authors' series of cases of hyperthyroidism are explained by a twofold mechanism; first, by an association with overactivity of the vagus and the consequent rapid emptying of the gastric contents as well as the subsequent duodenal regurgitation; the other, by a direct inhibitory action of the sympathetic on hydrochloric acid secretion, thus causing a true achlorhydria. Both the vagal and sympathetic types of achlorhydria may be ascribed to profound changes in the tone of the vagus and sympathetic nerves which are so well known in Graves' disease. Brown likewise investigated the influence of hyperthyroidism on the secretion of the free hydrochloric acid. It is his impression that hyperthyroidism produces an increased sympathetic drive which overbalances the normal moderator influence of the parasympathetic. This induces stimulation of the inhibitory influences which affect the gastric mucosa and result in a diminution or absence of gastric secretion.

According to Lerman and Means, patients with exophthalmic goiter have a definite lowering of the gastric acidity to about one-half its normal value. The actual incidence of achlorhydria in this affection is 38 per

cent. The frequency of achlorhydria is out of proportion to the depression in the average acidities and suggests that other factors are also important in its causation. According to these authors, there is perhaps a threshold of gastric secretion and if the secretion is depressed beyond it, anacidity results. In exophthalmic goiter there is no definite correlation between gastric acidity and such factors as age, red blood cell count, haemoglobin and level of basal metabolism. On the other hand, there is a high degree of correlation between the incidence of achlorhydria and age and basal metabolic rate and a probable inverse correlation between the incidence of achlorhydria and red blood cell count and haemoglobin.

According to our own experience hypochlorhydria and achlorhydria are usually observed in hyperthyroidism and exophthalmic goiter. This occurs in from one-third to over one-half of the cases. Of 20 patients affected with this condition achlorhydria was present in 9, hypochlorhydria in 4, normal acidity in 4 and hyperchlorhydria in 3. As gastric acidity is usually lessened in hyperthyroidism, the associated symptom of diarrhea may be an outcome of incomplete gastric digestion.

In hyperthyroidism the motility of the stomach is usually greatly increased or disturbed. In some instances there is a rapid emptying of the stomach; in others vomiting, frequently of bile, may occur and may be associated with nausea. The vomiting may occur in paroxysmal crises, without nausea and without relation to food. It may be uncontrollable for a time and then the attack may suddenly cease and be followed by a period of comparative comfort as regards the digestive functions. Hunger sensations may result from contractions of the empty stomach. Attacks of aerophagia are also common and pylorospasm is likewise frequently observed.

Recently Verbrycke (14) directed our attention to so-called masked gastro-intestinal hyperthyroidism. In these cases the thyroid plays an important rôle in the production of digestive symptoms without producing the usual thyroid syndrome and without demonstrable enlargement of the gland. In 34 patients who presented themselves for gastro-intestinal diagnosis, the cause of the symptoms was proved to be the thyroid gland, although there were many instances in which the thyroid was not suspected at the first examination. An analysis of the presenting symptoms of the patients revealed that "nervousness" occupied first place in 11 and general abdominal pain and cramps in 16; nausea and vomiting occurred in 9, weakness in 7, palpitation in 7, "gas" in 5 and diarrhea in 3 cases; 24 had lost weight. On examination, a rapid pulse was one of the first things to attract attention. The basal metabolic rate varied from plus 14 to plus 112 with an average of 45.8 per cent. A large proportion of these cases responded in a completely satisfactory way to medical measures.

That masked forms of hyperthyroidism are not infrequent has been pointed out by Hamburger and Lev (15), who describe certain signs leading to the diagnosis, but they do not refer very clearly to the gastro-

intestinal type. They state that the term masked hyperthyroidism is used to designate "a group of middle-aged, apathetic men and women in whom the classic signs and symptoms of hyperthyroidism are wanting but who present an atypical, clinical picture of some other type of disease, as organic heart disease, congestive heart failure, angina pectoris, diabetes or pernicious vomiting. This group bears a certain relation to the 'maladie de Basedow forme frustes' discussed in the literature."

"The diagnosis of masked hyperthyroidism, in addition to the points mentioned, rests on a suggestive increased warmth, redness or pigmentation of the skin, slight staring expression of the eyes, increased restlessness, unexplained loss of weight, persistent increase in the basal metabolic rate, improvement or relief of symptoms and decrease in the basal metabolic rate following iodine medication and thyroidectomy."

"It is important that this frequently undiagnosed or misdiagnosed group of cases be recognized in spite of the difficulties in diagnosis."

In our experience masked types of gastro-intestinal hyperthyroidism are not infrequent. The following history briefly represents an instance of this condition:

K. T. Female, aged 51 years, had always enjoyed good health until two years ago when, following the sudden accidental death of her husband, she began to suffer with extreme nervousness, depression, hysterical attacks, weakness, faintness, and palpitation. A month later her digestion became involved and she now began to complain of loss of appetite, discomfort in the abdomen, apparently due to gas, extreme constipation, the passage of mucus in the stools, occasional nausea and frequent paroxysmal attacks of vomiting. The latter, however, had apparently no relation to the ingestion of food and consisted largely of bile-stained fluid. The patient was treated for several months for "nervous indigestion and a nervous breakdown."

On physical examination but few abnormalities could be detected. There was a loss of 15 pounds in weight. The heart was rapid but otherwise normal, pulse 110 per minute, blood pressure 140/80. The abdomen was soft and extremely relaxed. An Ewald test meal revealed a total achylia. The stool contained considerable mucus but was otherwise normal. The basal metabolic rate was plus 34. A gastro-intestinal roentgen-ray series revealed a spastic gastro-intestinal tract together with a maximum prolapse.

The diagnosis of masked hyperthyroidism with gastro-intestinal involvement was made.

Only symptomatic treatment was directed to the digestive tract and nervous system, but more important was the administration of Lugol's solution in moderate dosage for short periods. The appetite soon improved, the digestive symptoms gradually disappeared and the patient made a rapid gain in weight of 10 pounds. She had apparently entirely recovered her health after several months and her basal rate had fallen to plus 12. The roentgen treatment as advocated by Verbrycke was not employed.

This case illustrates the fact that prominent digestive symptoms should not allow one to forget the possibility of thyroid disease, especially when the patient presents a flushed appearance with warm, moist skin, "nervousness," rapid pulse rate, slight staring of the eyes, tremor and loss of weight. These symptoms at once point to the true underlying cause of the marked gastro-intestinal upset as due to hyperthyroidism and this can then be verified by further investigations. Proper therapy can then be instituted.

The simultaneous occurrence of organic lesions of the digestive tract and hyperthyroid states must likewise be considered. Crile (16) has called attention to the high incidence of peptic ulcer associated with hyperthyroidism as well as with other endocrinopathies. Robertson and Hargis (17) have likewise demonstrated at autopsy the frequent coexistence of peptic ulcer in individuals with toxic goiter.

Finally, attention must be directed to the differentiation of thyrotoxicosis and the menopausal disturbances associated with gastro-intestinal dysfunctions. Severinghaus (18) has recently called attention to this condition. He points out that the determination of a single basal metabolic rate is not sufficient in differentiating the two conditions even when a complete physical examination has been made. The basal metabolic rate is perhaps the best criterion but even this may be confusing in these individuals unless at repeated determinations fairly constant high rates are obtained. Highly variable rates indicate that the condition is probably due to other causes than to thyrotoxicosis.

The following case illustrates this condition:

The patient, a female of 44 years, had been the victim of indigestion for years. She had had a true achylia extending over this entire period with loss of appetite, tendency to diarrhea, eructations, fullness and distention following meals. Under careful dietary regulations and with the constant use of hydrochloric acid, she maintained a fairly comfortable existence. Two months ago an irregularity of her periods became manifest. This was followed by paroxysmal hot flushes together with sweats, palpitation, vertigo, faintness and extreme nervousness. Her former digestive symptoms now became intensified.

Physical examination revealed a rather anxious and nervous female. The thyroid was not palpable, and although the eyes were somewhat prominent, none of the usual signs of Graves' disease could be detected. The heart was normal but rapid. The blood pressure was 125/80. Tremor of the hands was marked. The abdomen was soft, relaxed and there was distinct tenderness over the course of the descending colon. The gastric contents revealed a total achylia. The stool contained considerable mucus but was otherwise normal. The basal metabolic rate was plus 64. The diagnosis of hyperthyroidism with secondary gastric disturbance was made and the patient was placed at rest and Lugol's solution prescribed but without apparent relief. However, following the administration of phenobarbital, together with specific glandular (amniotin) extract, the symptoms rapidly subsided with a gradual lowering of the basal rate to plus 14.

It is quite evident that the gastro-intestinal symptoms in this instance were produced as a result of the menstrual disorder and were not due to a thyrotoxicosis.

The intestinal disturbance most commonly observed in hyperthyroidism is diarrhea. This may occur at the onset preceding the usual symptoms and may be present in the form of crises. It may be transitory or permanent and, if the latter, the prognosis is rendered far more serious. Diarrhea may occur both in the early and late stages of the affection. The stools are watery, varying in number and frequency from one or two to 20 or 30 a day. According to Sattler (19), these attacks are observed in at least 30 per cent of cases of hyperthyroidism. The stools are discharged without pain and without relation to the ingestion of food. They

may be uncontrollable for a time when the diarrhea may suddenly cease and the stools become normal or even constipated. Alternating diarrhea and constipation may likewise occur. The diarrhea may even take the form of so-called "morning diarrhea," characterized by the discharge of many movements in the early morning hours. The presence of the frequent liquid discharge may be so prominent as to entirely obscure the signs relating to the thyroid and thus lead to an incorrect conclusion as to its cause unless a meticulous clinical investigation be undertaken.

It is quite possible that many of the so-called nervous diarrheas commonly observed in young females may be due to the presence of a thyrotoxicosis.

In the more serious cases the diarrhea may be associated with nausea and vomiting and, in fact, at times the latter may alternate with the former. In the less violent forms the appetite may continue to be normal or even become ravenous and in spite of the mildness of the diarrhea the patient will continue to lose weight.

The stools are liquid, often highly bile-stained and, at times, contain undigested food remains and later on mucus and even blood due to the development of a mucous or even an actual ulcerative colitis.

The diarrhea of hyperthyroidism is attributed by Eppinger and Hess to vagotonia, i.e., overactivity of the vagus nerve, while others consider it the result of the commonly associated achylia gastrica. It may, however, be produced as a direct effect of the thyrotoxicosis itself upon the motility of the bowel.

2. GASTRO-INTESTINAL MANIFESTATIONS INCIDENT TO HYPOTHYROIDISM

The gastro-intestinal manifestations occurring in hypothyroidism include, according to Barker, disturbances of the salivary secretion, of the appetite, of dentition, of gastric secretion and motility, of intestinal secretion and motility, and of metabolism.

In hypothyroidism (myxedema and myxedematous affections) the salivary secretion is thickened and becomes diminished, producing a dryness of the mouth. The tongue is thick and dry. The appetite is ordinarily decreased, often to a degree of intense anorexia. The teeth are usually in poor condition, often decayed, and pyorrhea is not infrequently observed.

The gastric acidity is usually diminished in hypothyroidism. In a single case of Barker's, a complete achylia was found. Lockwood observed an achlorhydria in 6 of 10 cases and Brown (20) in 4 of 10 cases. Sturgis (21) reports his gastric analyses in five instances of myxedema, in three of which there was an achylia, in one a low acidity and in the other a normal acidity. Lerman and Means find the incidence of achlorhydria in myxedema 53 per cent in a study of 17 patients. In this condition there is an unusual tendency to anemia among patients with achlorhydria. There is indirect evidence according to these authors that achlorhydria may per-

sist at least in some cases after the primary condition has been cured. Knowledge of the state of the gastric secretion in an individual case may be of practical importance in preventing the onset of anemia.

According to our experience achlorhydria and hypochlorhydria are even more frequently observed in hypothyroidism than in hyperthyroidism. Of 20 patients affected with varying degrees of hypothyroidism achylia was present in 12, hypochlorhydria in 3, normal acidity in 3 and hyperchlorhydria in 2.

In hypothyroidism disturbances of motility of the gastro-intestinal tract are common. There is usually a definite atony especially referable to the intestine leading to a severe grade of constipation.

The symptoms which may lead to the diagnosis of hypothyroidism are usually indefinite and vague unless the condition be advanced to a distinct myxedematous state. Those leading to a suspicion of this affection are nervousness, mental depression and inactivity, inability to concentrate, loss of memory, falling of the hair and dry skin. The diagnosis can, however, be more certainly arrived at if, together with the above mentioned symptoms, a definitely lowered metabolic rate is noted. The gastro-intestinal symptoms of hypothyroidism, however, are still more uncertain. Of these, the one already referred to (chronic constipation) is most striking. The constipation may become so severe that many days may pass by without movements. This condition arises as the result of an atonic state of the bowel due, according to Falta (22), to a decreased tonus of the vegetative nervous system leading to a persistent paresis and retention of toxic products. Brown points out that hypothyroidism, especially if the basal readings are very low, leads to intractable constipation which is not overcome by the usual methods of treatment. It is not infrequently observed in women in the late forties or fifties. He deems it advisable to suspect at least the presence of an unrecognized hypothyroidism in individuals of this type who have intractable constipation.

Our experience confirms the findings of Brown and has led us to the conclusion that the intractable forms of constipation due to hypothyroidism also occur occasionally in obese men as well as in young individuals of both sexes.

An instance of intractable constipation due to hypothyroidism is presented in the following case.

The patient, a female of 46 years, had been affected with an increasingly severe constipation for the past five years. Previous to this period, constipation was frequently present, but could be easily regulated by the use of mild laxatives, and there were frequent intervals during which normal evacuations occurred without the aid of drugs. During the past year, constipation became so severe that even the strongest laxatives frequently failed to give relief. In addition, the patient was frequently disturbed by indigestion, characterized by pressure and fullness following meals, eructations and occasionally nausea. The menopause occurred normally 3½ years ago, and since then she has gained 25 pounds in weight. The patient complains likewise of nervousness, depression and loss of memory.

Physical examination revealed a rather obese individual. The thyroid was not palpable; the skin was dry, but no other signs of myxedema were present. The heart was normal, blood pressure 120/80. The abdomen was soft, extremely relaxed and of the enteroptotic type; no evidence of tenderness could be detected. The gastric contents presented an achylia. The stools were large in calibre and contained considerable mucus but were otherwise normal. A gastro-intestinal roentgen ray series revealed a marked enteroptosis, but no other abnormalities. The basal metabolic rate was minus 18. The diagnosis of hypothyroidism with secondary chronic constipation was made. The use of thyroid extract medication (½ to 1 grain three times daily) together with moderate doses of mineral oil soon resulted in normal bowel function. As a further evidence that the hypothyroid state was largely responsible for the constipation was the return of the intense constipation whenever the thyroid extract was omitted.

Hinton (23) has recently called attention to an equally important symptom, namely, abdominal pain, due to hypothyroidism. He emphasizes the fact that certain patients who suffer pain simulating peptic ulcer or cholecystitis and who present negative laboratory findings may in a small percentage of instances be affected with a hypothyroid disturbance. In all such instances a metabolic determination should be made prior to the institution of treatment. The author points out distinctly that this condition occurs only in a small group of cases and that a patient may have both a low basal rate and an intra-abdominal lesion requiring either medical or surgical treatment.

Many of the individuals affected with hypothyroidism are the subjects of visceroptosis of a greater or lesser degree which may give rise to functional digestive disturbances in the form of gas, pressure and fullness in the abdomen. A coexisting chronic appendicitis is not an uncommon complication. According to Barker, children affected with congenital myxedema may frequently have a tympanitic abdomen and may be pot-bellied. Umbilical hernia is occasionally observed as well as prolapse of the rectum. Rectal hemorrhages and hemorrhoids are not uncommon in adults with myxedema.

TREATMENT OF THE GASTRO-INTESTINAL DISTURBANCES DUE TO DISTURBED THYROID FUNCTION

The treatment must necessarily be directed towards overcoming the thyroid dysfunction. Inasmuch as the metabolism is greatly increased in hyperthyroidism rapid emaciation is produced notwithstanding the fact that the patient may continue to consume excessive quantities of food. The food elements, including protein, carbohydrates and fats, are rapidly metabolized. The emaciation is further increased by the vomiting and diarrhea. In order to overcome, as far as possible, the ravages of the disease, it is highly important to have the patient placed at rest in bed under as nearly ideal hygienic and psychic control as possible, and this can usually be best accomplished in a hospital. A high caloric diet should be prescribed as a gain in weight is essential for recovery. Moll (24) advocates a diet rich in carbohydrates as most beneficial. Fatty diarrhea with lowered carbohydrate tolerance is occasionally met with and requires special dietetic care.

Phenobarbital or the bromides are utilized as sedatives in moderate doses to overcome the nervous irritability and to induce sleep. Quinine hydrobromide and hypodermic injections of sodium cacodylate are of great value. Small amounts of Lugol's solution should be prescribed for short periods. Ordinarily no further treatment is indicated to overcome the digestive symptoms as these will gradually disappear with the improvement of the patient's general condition. The administration of muriatic acid is beneficial in those instances in which the achylia is associated with diarrhea. In the intractable forms of vomiting relief has been obtained by means of duodenal feeding.

The diarrhea has been alleviated in a number of our patients by the administration of adequate doses of pancreatin combined with calcium carbonate. Verbrycke advises the use of roentgen treatment as an aid in overcoming the gastro-intestinal symptoms due to hyperthyroidism. Inasmuch as the parathyroids are irradiated at the same time, care must be exercised to avoid a permanent disturbance of the latter. It is quite possible, too, that due to this form of treatment, with the resulting adhesions and fibrosis, subsequent surgery of the thyroid may be made more difficult.

Frequent basal metabolic rate determinations are required in order to decide definitely whether improvement is taking place or whether surgery is indicated.

In hypothyroidism (myxedematous states) the metabolic processes are diminished and although the patient may consume but small amounts of food, increase in weight is noted. The total metabolism, including that of the proteins, fats and carbohydrates, is reduced. The carbohydrate tolerance is greatly increased. The indication in this affection is, therefore, to stimulate the metabolic processes. This can only be imperfectly accomplished by means of a reduction in the food intake alone.

Thyroid extract is indicated in the treatment of hypothyroidism. This remedy should be administered cautiously and the dosage regulated according to the patient's condition. Thyroid extract, or in certain instances thyroxine, not only relieves the general symptoms due to this condition itself but the gastro-intestinal manifestations as well. Brown advises its use in the cases of intractable constipation due to masked hypothyroidism already referred to and Hinton advises its use in alleviating abdominal pain due to the same condition. In both, our experience has been that its administration is followed by signal success.

Lahey (25) has recently called attention to the fact that there are patients with low basal rates who are not benefited by thyroid extract. These have basal rates of minus 25 or less. He has observed that only those patients having a definite hypercholesterolemia, that is, a blood cholesterol of 200 or over, are improved by thyroid medication, while those with a normal cholesterol but with moderate degrees of minus basal rates will not be benefited by such treatment. Lahey considers this method of great value inasmuch as it enables us at once to separate those patients

with low basal rates in whom one can anticipate benefit as the result of thyroid extract from those in whom this remedy is of no value.

In the latter group, usually with low rates of minus 20 or less, the symptoms are largely the result, according to Eusterman (26), of a psychoneurosis or constitutional inadequacy. This group manifests certain functional gastro-intestinal disturbances in which thyroid medication is often of little or no value. Treatment should be directed in these instances to a general up-building of the patient's health as well as his nervous system.

THE DIGESTIVE TRACT IN PARATHYROID DISEASE

The gastro-intestinal disturbances occurring in parathyroid disease have not as yet been clearly defined. As a result of parathyroid dysfunction, Barker calls attention to the following digestive symptoms: enamel defects in parathyroid insufficiency, variations in calcium metabolism, gastric tetany, Barker and Estes syndrome (i.e., chronic dilatation of upper gastro-intestinal tract, tetany and hematoporphyrinuria), disturbance of salivation in tetany, spasm of the smooth muscle fibers of the gastro-intestinal tract in tetany.

In parathyroid insufficiency there is an increased elimination of calcium and it is commonly known that the convulsions induced by the removal of the parathyroids can be controlled by the administration of calcium salts.

According to Barker (6), gastro-intestinal disturbances are frequently observed in tetany. These may be of two types; one occurs in patients affected with chronic gastric disease and the other in patients in whom the digestive upset appears at the time of onset of tetany.

In the first form, so clearly described by Kussmaul (27) the digestive disturbance has been present for a long time and then tetany suddenly develops. In these cases pyloric or duodenal stenosis has often existed for many years with gastric stagnation of a high degree. Occasionally atonic dilatation without stenosis has led to the same condition. The tetany is probably due in some way to an alkalosis induced by the stagnation for it has been observed that lavage of the stomach sometimes causes a remission. In the second form in which gastro-intestinal symptoms develop at or following the onset of tetany, the patients develop hyperexcitability of the stomach and increased gastric secretion with high acidity and stasis often associated with diarrhea. The gastric contents in both the first and second conditions is usually of the three-layered type and contains yeast spores and sarcinae in abundance.

Barker and Estes (28) have described another form in which chronic dilatation of the upper gastro-intestinal tract occurs accompanied by tetany and hematoporphyrinuria. This condition was observed in three sisters. Tetanic seizures may likewise occur in upper intestinal obstruction as a result of the intoxication associated with varying degrees of alkalosis.

The following case of gastric dilatation in which tetanic seizures occurred is of interest.

The patient, a male of 48 years of age, had had gastric dilatation for a period of eight years. The condition followed the healing of an old pyloric ulcer. He refused operation and could only be kept free from symptoms of indigestion (nausea, vomiting, abdominal discomfort and eructations) by means of daily gastric lavage. At varying periods this procedure was omitted for two to three weeks at a time and, in consequence, vomiting of the retention type occurred. A most careful dietetic regimen was constantly maintained. Recently, after a period of three weeks in which lavage had been omitted, vomiting of a similar type began. This was followed by a toxic state, lasting a few hours, during which the patient refused nourishment, became drowsy and difficult to arouse. Suddenly typical attacks of tetany developed. These consisted of tonic spasms in the hands and arms, followed immediately by a similar condition in the legs, and with distortion of the muscles of the face. The attacks lasted a few minutes and were followed by numerous successive attacks, lasting altogether about two hours. Such attacks occurred from time to time at varying periods, even in spite of lavage. They were finally overcome by the administration of parathyroid and calcium therapy. The patient was subsequently operated upon for an acute perforation of the ulcer, but he died as a result of it.

It is held in addition by some observers that the problem of allergy is in some way closely related to the endocrine system, and especially with the parathyroid and calcium metabolism. The satisfactory results of treatment in allergic conditions from the use of parathyroid and calcium or from adrenal therapy tends to confirm this view. A factor which may be of importance in the production of these symptoms is the close proximity of the thyroid and parathyroids for this makes it conceivable that the two glands may be involved simultaneously and thus give rise to a varied combination of symptoms.

Spasm of the musculature of the digestive tract may occasionally be produced in tentany due to increased tonus of the vegetative nervous system. As a result pyloric spasm may occur of so high a degree in the acute stages of this affection as to lead to actual dilatation of the stomach. Spasm of various parts of the intestinal tract has likewise been described. Moreover, gaseous distention due to colonic spasm and involvement of the anal sphincter may be produced. A diminished parathyroid activity induces spasticity due to its effect upon calcium metabolism, while an increased action produces nausea and vomiting.

In the treatment of parathyroid deficiency affections, the administration of parathyroid extract (parathormone) and calcium salts is indicated. Whenever dilatation of the stomach occurs, lavage should be performed and if there be the slightest tendency to an alkalosis and tetany saline solution and dextrose should be given parenterally.

In obstructions of the upper intestinal tract with impending toxaemia and tetany a similar form of treatment must be instituted before operation is undertaken.

THE DIGESTIVE TRACT IN PITUITARY GLAND DISEASE

Disturbances of function of the pituitary gland may be due to overactivity or underactivity. A combination of the two is, however, frequently present leading to the condition recognized as dyspituitarism. In discuss-

ing the affections associated with this gland Barker gives the following classifications:

(1) The hypophysis and splanchnomegaly.

(2) Thirst in diabetes insipidus.

(3) Effect of pituitrin upon the smooth musele of the intestine.

(4) Hypophysis and carbohydrate metabolism.

Disturbances of the teeth as well as the soft tissues of the gastro-intestinal tract are produced due to oversecretion of the anterior lobe of the gland. As a result of the enlargement of the mandibles the teeth become farther separated from one another. Thickening of the tongue, lips and the mucous membranes of the buccal cavity is likewise noted. Hypertrophy of the walls of the stomach and intestine has been described as well as enlargement of the liver, pancreas, and spleen. Dilatation of the stomach likewise occurs frequently associted with polyphagia. A marked increase in the length of the small intestine has likewise been reported.

The gastric secretion presents no consistent change in pituitary disease. Hyperchlorhydria has ordinarily been noted, though Lockwood found an achylia in three cases of hypopituitary disease.

Increased thirst is a pronounced symptom of diabetes insipidus (due to disturbance of the pars intermedia) and this can be controlled by means of the hypodermic administration of pituitrin.

Pituitrin has likewise a direct effect upon the musculature of the intestine. It produces an immediate slowing of the peristaltic movements both as to rhythm and tone which is quickly followed by a powerful increase of the movements. According to Bayer and Peter (2) the preliminary phase is due to stimulation of the sympathetic fibers inhibiting the muscles, the second to stimulation of Auerbach's plexus and of the post-ganglionic fibers. Galan's (29) observations have led him to conclude that the extract has an exciting action upon gastric tonus. Ginsburg and Tumpowsky (30) found that one cubic centimeter of pituitary extract caused immediate inhibition of hunger contractions lasting over a period of from one to two hours.

Pancoast and Hopkins (31) investigated the effect of the pituitary extract on the gastro-intestinal tract by means of roentgen-ray studies. The results were not entirely conclusive. In general, there was a primary decrease followed by an increase in gastric motility. There was ordinarily but a slight change in the small intestine but occasionally it was increased. It is now well established that this extract produces an intense peristalsis of the colon.

According to Barker, the pituitary gland plays a rôle in the control of carbohydrate metabolism inasmuch as acromegaly is frequently associated with glycosuria or diabetes mellitus and as dystrophia adiposo-genitalis is associated with rapidly developing obesity.

Strauss (32) has observed the onset of intestinal disturbances associated with dystrophia adiposo-genitalis. The syndrome appeared in the form of diarrhea, frequently with pain, which alternated with constipation. The condition manifested itself in the nature of a ceco-colonic inflammatory process and has been not uncommonly observed in otherwise healthy, though nervous, individuals in middle life. The cecum afterward appeared like a blown-up rubber bag and in many instances was tender on pressure. In the largest proportion of cases the roentgen-ray revealed an atony of the cecum with a lowering of its pole and abnormal mobility. The cases observed were in males with more or less marked degrees of micro-genitalism, most of whom presented signs of dystrophia adiposo-genitalis. The author seeks an explanation in the dysfunctioning of the glands of internal secretion, in vegetative hormonal or vegetative neurogenic influences, having especially in mind the hypophysis and the midbrain.

In the treatment of the digestive disturbances due to pituitary disease pituitrin performs an important service. It restores tone to the functionally obstructed bowel and overcomes the distension and constipation due to this condition. It likewise overcomes the thirst and polyuria observed in diabetes insipidus.

THE DIGESTIVE TRACT IN ADRENAL DISEASE

Adrenaline when injected intravenously stimulates the terminal sympathetic fibers of the glands and muscles. It acts directly upon the musculature of the gastro-intestinal tract, causing relaxation by arresting peristalsis. It also stimulates contractions of the sphincters.

Rogers (33) and his associates observed that injections of epinephrine and the suprarenal nucleoprotein inhibit gastric secretion, while Ginsburg and Tumpowsky (30) found that 1 cc. of 1 to 10,000 solution of epinephrine caused a marked inhibition of hunger contractions in one to two hours. Even when injected subcutaneously it increases blood pressure and may produce hyperglycemia and glycosuria.

The relation of the adrenals to the production of peptic ulceration has been a matter of considerable interest. It is well known through the experiments of Mann (34), Friedman (35), and others that following removal of the suprarenals peptic ulcer may follow in some cases.

This lesion has been considered dependent both upon adrenal insufficiency and excess of adrenaline as the result of alternating hypo- and hyper-function of the gland. Friedman suggests that there may be some correlation between thyroid and adrenal secretions. More recently Crile (36) in several publications likewise points out the combined influence of the thyroid, adrenal and nervous system (psychic factor) in the production of peptic ulcer. He summarizes his observations as follows: "We find that peptic ulcer, like hyperthyroidism, is a unique human product bred in the atmosphere of stress and striving; that it is influenced by infection,

emotion, work, worry—by anything that causes increased nerve, thyroid and adrenal activity; this in turn resulting in gastric hyperacidity, and this hyperacidity in turn causing an increased electric potential, which in turn leads up to increased motility and electrolysis, with resultant ulcer. In myxedema, on the other hand, there is low or no gastric acidity, low potential, sluggish digestion, no electrolysis, no ulcer." He concludes (1) that "experimental evidence indicates that the nervous system and the thyroid and adrenal glands control gastric acidity and potential difference, and that hyperacidity produces peptic ulcer, the immediate physical agency being electrolysis, due to a high potential. (2) Peptic ulcer can be controlled by excision of enough of the thyroid gland to produce hypothyroidism and administration of enough thyroid extract to permit normal function. (3) Better results are obtained by removal of part of the thyroid and one adrenal gland. (4) In five cases of intractable or recurrent ulcer of the stomach, unilateral adrenalectomy and partial thyroidectomy decreased gastric and intestinal motility, followed by disappearance of symptoms."

The interrelation of the suprerenals to other glands in the form of functional antagonism has been fully recognized. Smithies (37) emphasizes the importance and significance of the antagonism between the suprarenals and the pancreas. He points out that when the suprarenal is speeded up there follows an acute hyper-suprarenalism and a depression of the pancreatic function. It is possible that some of the diarrheas in hyper-thyroidism are in some degree due to the associated hypo-functioning of the pancreas resulting from a speeding up of suprarenal function. On the other hand, as diminution in function of the thyroid occurs, continuance of the overfunctioning of the suprarenal may persist. This hypersecretion of epinephrine leads to a spasticity of the non-striated muscles of the splanchnic areas giving rise to marked spasticity in the bowel. This spasticity may produce obstinate constipation and perhaps a tendency to functional obstruction. Smithies calls attention to the fact that in those patients affected with diarrhea this condition may be alleviated by the early administration of large doses of pancreatin combined with calcium carbonate. The spastic conditions yield to belladonna together with a calcium salt.

As a further involvement of the suprarenal gland a lesion in the cortex is recognized to be the cause of Addison's disease. In this affection digestive symptoms are pronounced. They consist of attacks of intolerance to food, anorexia, fullness and distention following meals, eructations, nausea and vomiting. Constipation, present at first, is finally displaced by violent attacks of diarrhea and the two conditions may alternate. In the late stages of the disease, the diarrhea occurs in crises of such intense severity as to lead to collapse, coma or delirium. Epigastric pain is frequently observed together with rigidity of the abdominal muscles and the abdomen becomes retracted. At first the pain may be paroxysmal in type but finally

becomes more constant and with it vomiting is excessive especially in the terminal stages. The vomitus contains bile and mucus and occasionally traces of blood.

The gastric contents present no abnormality in the early stages of the disease but finally free hydrochloric acid becomes diminished and in the later stages achlorhydria is the characteristic finding.

In the treatment of the digestive disturbances due to suprarenal disease, epinephrine is found useful for the relief of visceral spasm in some instances. In the so-called suprarenal dyspepsia described by Loeper (38) and characterized by atony of the gastro-intestinal tract together with hypochlorhydria daily injections of adrenaline have been found useful.

Whenever the cortex of the adrenals is involved as in Addison's disease injections of the recently introduced cortin produce brilliant results in eliminating the digestive symptoms as well as the ravages of this disease and thus this therapy prevents the hitherto rapid and fatal outcome.

The digestive symptoms of Addison's disease are well illustrated by the two following cases.

The first patient, a male of 53 years, had been complaining of weakness and fatigue for the past year. These symptoms had become progressively severe, notwithstanding the fact that he had taken an unusual amount of rest. More recently he had noted a change in skin pigmentation, so that it took on a deep brown color, especially in the face, mouth and hands. With this, nausea and vomiting occurred in attacks, occasionally accompanied with epigastric pain. Anorexia was persistent and diarrhea frequently occurred.

On examination he presented the appearance of a feeble, debilitated individual with a weak pulse and a systolic blood pressure of 80. There was present a discoloration of his skin, especially of his hands, face, and the region of his nipples and genitals. There was a definite darkened pigmentary change in the mucus membrance of the mouth. The heart sounds were feeble, but regular. The abdomen was retracted, but no tender areas could be detected. A mild secondary anemia was noted; the vomiting and diarrhea became excessive and constant. The gastro-intestinal symptoms soon became aggravated; the cardio-vascular asthenia more intense; the pigmentation more pronounced.

The gastric contents presented an achlorhydria and contained bile and mucus.

The patient was confined to bed and injections of adrenaline administered cautiously, but notwithstanding these he became persistently weaker and his symptoms more pronounced. He died as the result of the asthenia within three months. This was before the days of cortical therapy.

The second is a very interesting case of R. L. S. male, aged 53 years, who complained of a constant dull ache in the stomach, with sourness, nausea, vomiting and excessive gas. His appetite had been variable. These symptoms were present for a few years.

On examination there was evidence of loss of weight (30 pounds in the past two years). He had a sallow complexion with no definite pigmentation of the skin. The abdomen was full and tense. The liver and spleen were not enlarged, and there was very little abnormal pigmentation of the abdomen. The heart and lungs were normal and the blood pressure was 150/85. There was a secondary anemia and an achylia. Roentgen-ray studies showed a cow-horn stomach, with the pylorus and duodenum pulled to the right and under the gall bladder. There was definite evidence of adhesions in the gall bladder region. At that time the impression was achylia gastrica, with cholecystitis. He was placed under treatment and subsequently developed symptoms so clearly related to gall bladder dysfunction that an operation was advised. Doctor Finney performed the operation and found the gall bladder to be normal and for that reason he did not remove it. Shortly after the recovery from the operation it was noticed that the blood pressure gradually fell. The skin took on a brown discoloration. The appetite became extremely poor; diarrhea developed; pigmentary patches in the mouth were seen. Finally the pressure fell to a systolic of

80. It was obvious at this time that the patient definitely had Addison's disease and therapy was directed towards that disease in the form of hypodermic injections of adrenalin, which were followed by considerable improvement. (Cortical extract was not available at this time). The improvement continued as long as the injections were administered. Later a combination of pituitary extract and adrenalin was given orally without much effect. Subsequently the patient developed acute attacks of severe abdominal colic somewhat similar to Dietl's crises, but nothing abnormal could be detected in the urine at any time; (these attacks have been described as an occasional concomitant of Addison's disease). The patient's condition was so poor that further investigation of these attacks could not be insituted. He gradually became weaker, and within a period of two months he succumbed. Unfortunately, no autopsy could be obtained.

THE DIGESTIVE TRACT IN DISEASES OF THE GONADS, THYMUS AND PINEAL GLANDS

Diseases of the gonads, thymus and pineal glands play an unimportant and indefinite rôle in the production of digestive symptoms.

Disturbances of the internal secretion of the gonads lead to changes in the carbohydrate metabolism producing an increased carbohydrate tolerance.

Changes in the thymus gland are responsible for hyperplasia of the tonsils and of lymphatic nodules in the digestive tract. An abnormally lengthened intestine has also been observed in this condition. Abnormal functioning of the pineal gland rarely gives rise to digestive disturbances, but it is interesting that Cushing (39) has found certain areas of the brain which are related in some causative way to the production and perforation of peptic ulcers. It is demonstrated, for example, that disturbance of the inter-brain due to an encroaching tumor or perhaps to trauma associated with brain operations as well as to other intracranial diseases and injuries may result in acute perforative lesions of the esophagus, stomach or duodenum. Cushing believes, however, that these perforations are probably produced by an irritative disturbance of fiber tracts or vagal centers in the brain stem and it therefore hardly seems possible that endocrine glands play a rôle in this phenomenon.

CONCLUSIONS

(1) The endocrinopathies play an important rôle in the production of digestive disturbances. The glands chiefly concerned are the thyroid, parathyroids, pituitary and adrenals.

(2) Hyperthyroidism gives rise to diarrhea and increased metabolism and digestive symptoms which can often be held in check by the use of Lugol's solution together with proper hygienic measures, rest, etc. When these procedures fail thyroidectomy is indicated. Hypothyroidism is associated with constipation and decreased metabolism and these in addition to other symptoms can be controlled by the use of thyroid extract or thyroxine.

(3) Parathyroid deficiency is closely related to disturbances of calcium excretion and tetany is observed in gastro-duodenal dilatation and

upper intestinal obstruction. Calcium salts and parathyroid extract (parathormone) are indicated in these conditions and salt solution and glucose when dilatation occurs with alkalosis.

(4) Disturbances of the pituitary gland give rise to obesity, enlargement of the abdominal organs and to increased thirst associated with diabetes insipidus. Pituitrin restores tone and may overcome functional bowel obstruction, distention of the bowel and constipation.

(5) The suprarenals inhibit peristalsis and the relation of peptic ulcer to suprarenal dysfunction is emphasized. In Addison's disease in which the cortex is involved marked gastro-intestinal symptoms are produced. Epinephrine has been found of value in relieving visceral spasm and cortin in the treatment of Addison's disease.

(6) It has been definitely established that a functional relationship exists between various endocrine glands and that a dysfunction in one frequently develops a change in function in another so that the cause of the production of gastro-intestinal symptoms is at times difficult to discover.

(7) Much has been accomplished but much still remains to be learned regarding the action of certain endocrine glands upon the functions of the digestive tract. When many of the difficulties surrounding this important problem have been solved it is to be hoped that the path will be cleared for a better understanding of the digestive disturbances due to the endocrinopathies.

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OESTROUS REACTIONS IN FEMALE RATS UNITED WITH CASTRATE PARABIONTS*

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INTRODUCTION

Several investigators working with parabiotic rats have shown that certain definite results can be obtained from such experiments, though there is a large amount of existing data with regard to vaginal smears and ovarian histology which appear to have but little semblance of consistency among them. The writer has made a histological study of the genital tissues from twenty-four pairs of female parabiotic rats, and has found definite facts concerning ovarian structure and oestrous cycles to be described later in this paper. It seems that a presentation of these findings at this time may serve to clarify some of the present misunderstanding concerning results for parabiosis experiments.

EXPERIMENTAL DATA

Martins ('29) has described experiments in which young female rats were united with castrate female littermates, with resultant long periods of oestrus in both members of the pairs. No statement is made, however, as to whether or not these animals had attained maturity previous to parabiotic union. Zacherl ('27), using a similar technique, states that both animals ceased oestrus. Contrary to both of these investigators, Fels ('29) observed prolonged periods of oestrus in the normal female and continuous dioestrus in the castrate. The author (Hill, '32) has already reported results quite comparable to those of Fels, but which do not agree with the observations of the previously mentioned authors, nor with the results of Kawashima ('31) and other workers. The cyclic curves of the pairs described here have been followed over long periods of time, and in part have been previously published (Hill, '32).

In order that a clear concept of the available data may be had and a critical correlation made, histological pictures of ovaries and corresponding graphic oestrous cycle charts from eight of these pairs are given. The pairs not figured in this paper show very similar characteristics. A photomicrograph of a cross section of one ovary of a rat which had been united parabiotically with a castrate male at 45 days of age (Fig. 1; pair 141)

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shows only excessive follicular development. The vaginal smears of the female show two normal oestrous cycles in ten days, followed by the onset of continuous heat (Fig. 3). Under identical conditions, the female of pair 143 went through three heat periods in 25 days, and a cross section of the ovary shows the presence of several large corpora lutea in its center (Figs. 2 and 3).

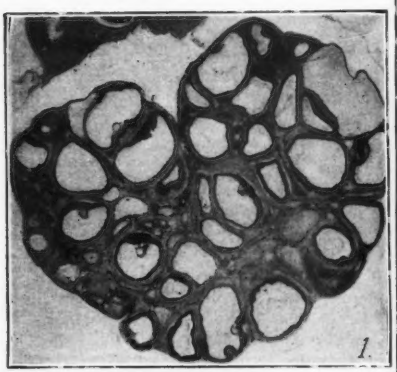

Figure 1. Photomicrograph of cross section of ovary from normal female of pair 141. (All magnifications are 11.8 times.)

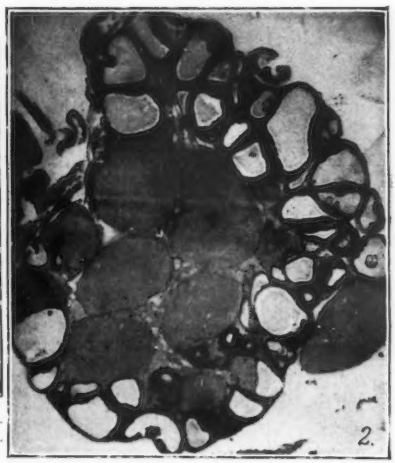

Figure 2. Photomicrograph of cross section of ovary from normal female of pair 143.

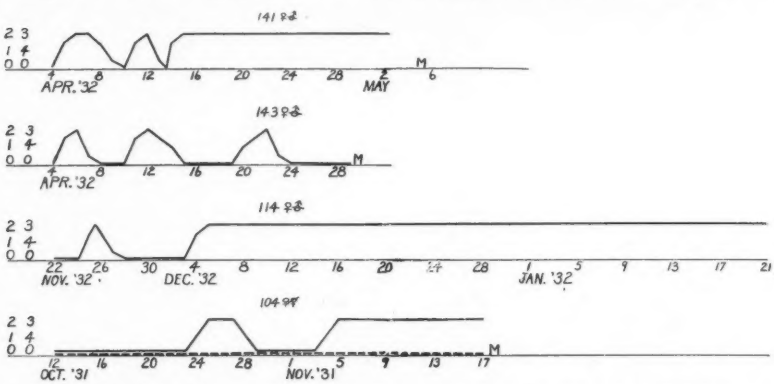

Figure 3. Oestrous cycle charts of pairs 141, 143, 114 and 104. Solid line indicates right animal; broken line, the left animal. The dioestral stage (0) lies on the base line, the ascending curve goes through pro-oestrus (1) to oestrus (2 and 3) at the peak, and the descending curve returns through metoestrum (4) to diestrus (0). M=death of pair.

A reaction very similar to that just described, having only a time variation, is represented by several parabiotic pairs of female-spayed female combination (Figs. 4, 5 and 8; pairs 107 and 40). The normal female of pair 40 gave but two cycles in 26 days in the presence of several large corpora in her ovaries. On the contrary and in the absence of a

significant amount of lutein tissue the female of pair 107 had entered upon continuous heat after a relatively short period of parabiotic life. However, it is well to notice that such an extended oestrous picture did not become apparent as soon as in those cases where the castrate parabiont was a male.

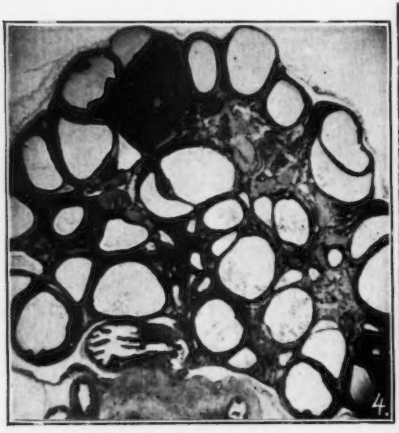

Figure 4. Photomicrograph of cross section of ovary from normal female of pair 107.

Figure 5. Photomicrograph of cross section of ovary from normal female of pair 40.

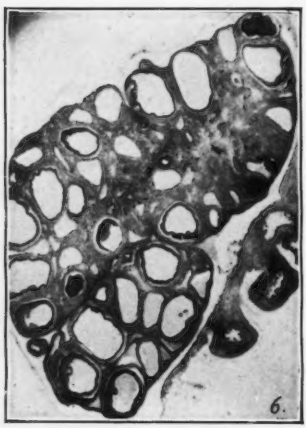

Figure 6. Photomicrograph of cross section of ovary from normal female of pair 114.

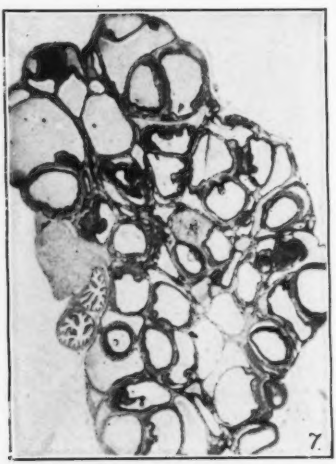

Figure 7. Photomicrograph of cross section of ovary from normal female of pair 104.

A comparative study of the time relation in the previously described reactions is made by considering the photomicrographs of the ovaries of pair 114 (a female with castrated male) and 104 (a female with spayed female) (Figs. 6 and 7) and their corresponding oestrus cycle charts (Fig. 3). The ovaries of the females in these two pairs exhibited a total absence

of lutein tissue. The female of pair 114 (with castrate male partner) attained continuous oestrus in approximately one-half the time required for the same reaction in the female united parabiotically to a spayed female (pair 104). This reaction may be attributed to the well proven fact that the gonadotropic potentialities of the anterior pituitary of the casrate male are greater than those of a spayed female.

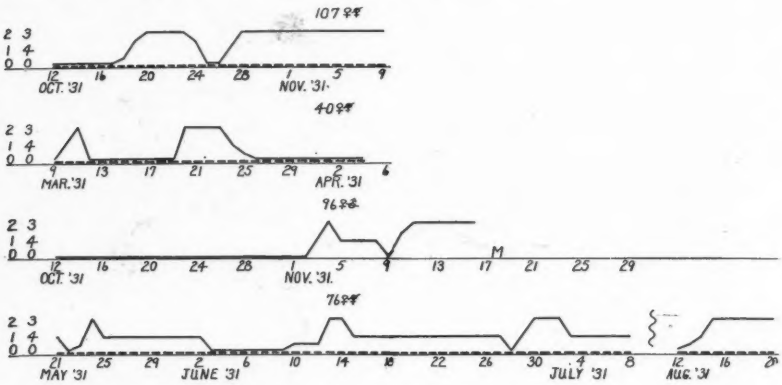

Figure 8. Oestrous cycle charts of pairs 107, 40, 96 and 76. Other legend same as for Figure 3. M=death of pair.

Another and yet more striking correlation of such potencies is seen in the following discovery. Those cases in which the ovaries of the female, in parabiotic union with a castrate partner, contain corpora lutea it is interesting to see whether or not the lutean tissue involutes, the time required and the conditions necessary. Figures 9 and 10 (pairs 96 and 76) show ovaries of the same general histological type. The female of pair 96 (with castrate male partner) required a total of 66 days to arrive at continuous heat (not completely shown in Fig. 8). On the contrary, the female of pair 76 (with spayed female partner) did not attain constant oestrus until the end of 130 days of parabiotic life (not completely shown in Figure 8).

Due to maturity the ovaries of both of these females probably contained active corpora at the outset of the experiment. In view of this it seems that perhaps additional corpora had not formed, that those already present involuted, and that constant oestrus did not become apparent until such regression was complete or nearly so. Coincident with these correlations two possible explanations present themselves. If the histological picture is an index of function, the rate of involution of the existing corpora is in proportion to the activity of the anterior pituitary of the castrate parabiont, being much more rapid if the gonadless partner is a male. On the other hand, the apparently well involuted corpora (Figs. 9 and 10) may still retain some portion of their original activity. If this be the case, then they seem to have reached the stage of involution and somewhat

decreased function until the gonadotropic potentialities of the castrate male anterior pituitary can, when compared to that of a spayed female, relatively soon override their action and cause the attainment of continuous oestrus in the normal female twin. This is graphically shown by the oestrous cycle charts of pairs 96 and 76 in Figure 8.

Figure 9. Photomicrograph of cross section of ovary from normal female of pair 96.

Figure 10. Photomicrograph of cross section of ovary from normal female of pair 76.

DISCUSSION

Consideration should be given to the question as to whether or not the corpora lutea seen in these experiments could have been formed after parabiotic union. A close examination of the tissues does not show evidence of recent ovulations. Also (Figs. 2 and 5), the corpora lie near the center of the ovaries and are quite well surrounded by a distinct follicular development. It seems probable, therefore, that the majority of the corpora lutea must have been formed either before parabiosis or before the pituitaries of the castrate parabionts have had time to exert their increased gonadotropic influence.

The follicles in the ovaries of such parabionts apparently never rupture. This statement is supported by the finding of sperm in the vaginal smear of some females at various intervals while in continuous oestrus, although no pregnancies ever resulted from such coitus. Whether the follicles of these ovaries go through atresia remains problematical for the present. It seems, at least, that if they involute they do not pass through a lutean stage.

A number of investigators have established proof that the gonadotropic potentialities of the anterior pituitary of the castrate male are greater than those of the spayed female. As previously pointed out the correlations made in this paper give additional proof of that fact. These con-

firmations are based on the comparatively shorter time required for continuous heat to be attained in the female if the castrate partner is a male. Furthermore, the more rapid lutean tissue involution, or the greater ability to override the reaction of lutean tissue which is decreasing in function is associated with a gonadless male as parabiont. More strength is added to this idea by Meyer (in press), who has united immature female rats in parabiosis with castrate littermates. By injecting oestrin into the castrate partner of his pairs the increase of the gonadotropic qualities of the anterior pituitary was inhibited, as noticed by the absence of any effect on the normal twin. This method has enabled him to determine (stated in rat units of oestrin necessary to inhibit) that the anterior pituitary of a castrate male is considerably more potent than that of a spayed female.

It is now possible to postulate what takes place during parabiosis when one partner is a castrate. In a normal female rat cystic ovaries can be induced by parabiotic union with a castrate partner through transfer of gonadotropic hormones from the increased output of the anterior pituitary of the gonadless parabiont. This reaction takes place sooner if the castrate partner is a male and is correlated with the comparatively rapid attainment of continuous heat in the female. If, on the other hand, a number of large corpora are present at the time the influence of the anterior pituitary of the castrate takes place, we find follicular development on the surface of the ovary and a tendency towards prolonged periods of dioestrus in the vaginal smears. The corpora lutea existing in the ovaries apparently undergo an involution which is associated with the increased function of the pituitary in the castrate parabiont. The function of the existing corpora lutea, whether by complete and more rapid involution, or by a steadily decreasing potency, has its action more quickly overridden if the gonadless partner is a male rather than a female.

The correlation of corpora in the ovaries and the tendency toward a dioestrous picture in the vaginal smear supports the opinion advanced in an earlier paper (Hill, '32) that the corpus luteum hormone transferred from a pregnant female to its parabiont tends to inhibit the occurrence of oestrus in the recipient.

SUMMARY

Twenty-four female rats were united parabiotically to castrate rats. Some of the castrate partners were males and some were females. The ovaries of the normal females were removed at various intervals after parabiotic union, and studied histologically. The histological data were correlated with the sex of the castrate partner and with the oestrous cycles of the normal parabiont.

It was found that those females exhibiting an absence of corpora in the ovaries soon arrived at continuous heat, having developed large cystic ovaries. This reaction appeared sooner (one-fourth to one-half the time) if the gonadless parabiont were a male instead of a female. This points

to the greater gonadotropic potency of the anterior pituitary of a castrate male than that of a spayed female.

If several large corpora were present in the ovaries of the normal females of these pairs the attainment of constant oestrus was very much delayed. However, it appeared in less time (one-fourth to one-half) if the castrate partner were a male rather than a female. The histological study showed the ovaries of the female of these pairs to contain completely involuted corpora in the medullary region with a cortical development of follicular cysts. From this a correlation is made between the greater potency of a castrate male pituitary and a more rapid involution of existing corpora. Constant heat did not occur when several large corpora were present in the ovaries, although the corpora remained apparently normal for some time and an extended follicular development took place in the peripheral zone of the ovary.

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THE FUNCTION OF THE CAROTID GLAND
(Glomus Caroticum)

1. THE ACTION OF EXTRACTS OF A CAROTID GLAND TUMOR IN MAN

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The carotid gland is still generally regarded as one of the paraganglia comparable to the glomus coccygeum and the aortic paraganglia of Zuckerkandl. "The carotid body is merely an outlying portion of the suprarenal system proper and might well be treated in connection with the accessory suprarenals and paraganglia" (Cowdry, 1922). This represents the usual text-book opinion of physiologists and pathologists alike. A review of the literature entirely fails to support such dogmatism, and one can only conclude that this is another misrepresentation of evidence which has been relayed from text-book to text-book. The excellent review of the literature up to 1900 by Kohn (1900) is generally quoted, and yet he states: "Seit vielen Jahren gegenstand lebhaften Interesse wurde sie histologisch and embryologisch vielfach untersucht ohne dass eine einheitliche Auffassung erzielt worden wäre." In the past 30 years evidence has been slowly accumulating that the Glomus Caroticum, or Carotid Gland, as we would prefer to call it, is independent of the suprarenal system.

In the human body the gland usually lies in the bifurcation of the common carotid artery or on the medial side of the upper end of the common carotid, in close proximity to the superior cervical ganglion. It is embedded in the fibrous tissue surrounding the carotid arteries, and is on an average 5x2½x1½ mm. in size (Lischka, 1862). On section the gland is seen to consist of groups of cells embedded in a rich sponge-work of capillaries, the whole being profusely infiltrated with nerve fibers. The following zones may be distinguished (de Castro, 1926; Riegele, 1928, etc.):

(1) Interstitial plexus consisting mainly of myelinated fibers of the glossopharyngeal and to a lesser extent the vagus nerves. There are also a few fibers from the superior cervical ganglion.

(2) Periglomerular plexus of non-myelinated fibers which pass from the interstitial plexus to envelop the cellular nests of the gland.

(3) Intraglomerular plexus of non-myelinated fibers passing mainly along the blood vessels to terminate between a cell surface and a capillary in the form of small or large rings. This plexus contains no sympathetic fibers, innervation of the cell islets being solely through the glossopharyngeal and vagus nerves, mainly the former. The sympathetic fibers in the interstitial plexus do not even approach the glandular cell islets.

(4) Glomeruli or cell islets consisting of irregular polygonal nucleated cells which are finely granular and vacuolar. One or more surfaces of the cell are in direct contact with a capillary, the reticulum of Golgi being situated at the pole nearest the nucleus and adjacent to the capillary. The cytoplasm is rich in lipoid but is negative to all tests for adrenaline (Vassale, 1912; de Castro, 1926; Aszoda and Paunz, 1923).

(5) Innervation is mainly through the glossopharyngeal and to a lesser extent through the vagus (Rabl, 1922; Gerard and Billingsby, 1923; Smith, 1924,

and de Castro, 1926 and 1927-28). These fibers reach the gland by way of the intercarotid nerve of Hering and run directly to the bulbar center from the nerve-ending in the gland without any intermediate ganglia. de Castro goes so far as to say that, in man at least, innervation of the gland cells is solely through these parasympathetic fibers.

As de Castro has pointed out, the morphology of the gland is strongly indicative of some active internal secretory function. He has summarized the evidence as follows: "(a) d'offrir un cytoplasme vacoulé, dont les vacuoles se trouvent à diverse degrés d'évolution, jusqu'à constituer de grandes vacuoles qui vont occuper la partie périphérique du corpuscule; (b) les modifications remarquées dans le noyeau quant à sa grosseur et à sa chromaticité, coincidentes avec l'élaboration de vacuoles, les variations du chondriome et des granulations lïpoides; (c) l'existence de granulations lïpoides et de grains imprégnables par l'ormium, variable en quantité de quelques éléments à d'autres; (d) l'orientation vers le pôle vasculaire du réticule de Golgi, posage peut-être de plus grand métabolisme du cytoplasme." It may be added that the gland is not a rundimentary or involutionary organ (Kohn, 1900; de Castro, 1926) and its complex structure and innervation certainly would indicate some active function.

The evidence against it being one of the sympathetic paraganglia is equally convincing: (a) The use of more modern and delicate tests for adrenaline in the gland has been negative (Vassale, 1912; de Castro, 1926; Aszoda and Paunz, 1923); (b) According to de Castro innervation of the gland is through the glossopharyngeal and vagus and not through the sympathetic. If these branches of the glossopharyngeal and vagus be cut and the animal sacrificed a few days later, an increase in the amount of lipoid in the cell can be observed. This is accompanied by a diminution of the mitochondria and chondriocontes (de Castro, 1926 and 1927-28; Rabl, 1922; Gerard and Billingsby, 1923; Smith, 1924).

Extirpation of the carotid gland has been claimed to lead to a variety of symptoms but unfortunately there is no conformity of results in the hand of different workers. Vassale (1912) has shown that extirpation of both carotid bodies in the cat invariably leads to a marked but transient glycosuria lasting from three to four days. This observation has been confirmed by Massaglia (1916), but considerable doubt has been cast on the significance of these experiments by Lanziolotta (1913), who showed that a similar glycosuria can be demonstrated after excision of the superior cervical ganglion, and that if the carotid glands are removed subsequent to this operation no such glycosuria results. He justifiably ascribes the glycosuria found by Vassale to trauma of the superior cervical ganglion. If the animals are observed for a longer period this glycosuria does not recur but in some cases the animals become cachectic with a tendency to alopecia. Betke (1915) and Fisher (1924) describe a train of symptoms appearing about five weeks after extirpation of the glands. These include listlessness, cachexia, alopecia, and impairment of growth, dentition and calcification of the bones. Scaffidi (Massaglia, 1916) and Klug (1924), on

the other hand, were unable to demonstrate any ill effects following extirpation of the carotid glands.

The same uncertainty exists as to the administration of extracts of the carotid gland. Frugoni (1913), with extracts from carotid glands of the calf injected intravenously into the rabbit, observed with moderate doses a slight rise in blood pressure followed by a fall of from 15 to 40 mm. Hg. This effect was much diminished on repeated injection. A single massive dose produced a profound fall in blood pressure followed by convulsions and a respiratory death, with complete incoagulability of the blood. Tolerance to such a massive dose could be greatly increased by the previous administration of smaller amounts. Frugoni realized that these results were typical of the effects of intravenous injection of any tissue extract. The doses used were enormous, representing one to two kilograms of gland substance. We have been unable to obtain any reference with regard to the methods he used for preparing the extracts, but the massive doses used would surely indicate that the gland was not isolated but the area around the bifurcation of the carotids merely excised. Even if the gland of the calf be twice the size of that found in the human (40 cub. mm.), it would require approximately 50,000 calf glands to supply his maximum dose of 2 kilograms! He admits that the results obtained were identical to those obtained with other tissue extracts, and we can only say that his experiments can have no direct bearing on the function of the carotid gland. Mullon, using extracts from the carotid gland of the horse, is quoted by de Castro (1926) as having obtained effects on the blood pressure similar to adrenaline. No reference is given and we have been unable to find any such article in the Index Medicus.

Jacobovici, Nitzescu and Pop (1928) claim that stimulation of the carotid gland produces a fall in blood pressure. No attempt was made to shield the carotid sinus from stimulation so we cannot see that their experiments are of any significance in relationship to the carotid gland.

Bouckaert, Dautrebande and Heymans (1931) have suggested that the carotid gland is sensitive to chemical stimuli (anoxaemia, CO_2, nicotine, lobeline, etc.), and is responsible for the reflex changes in blood pressure and respiration which had been previously ascribed to the sinus carotidis. The evidence they present for this hypothesis is suggestive but hardly conclusive. They claim that denervation of the sinus carotidis at the level of the bifurcation of the carotids abolishes its sensitivity to hydraulic but not to chemical stimuli, while denervation ½-1 cm. higher up abolishes sensitivity to both. The published tracings, however, do not indicate that sensitivity to hydraulic stimuli was ever completely abolished by denervation at the bifurcation. Also, although the carotids themselves were ligated, the vascular attachments of the carotid gland were left intact, so that the chemical simulation might be a central one. However, any contribution by Heymans and his associates to the physiology of the sinus carotidis is not to be disregarded and these experiments have been indirectly confirmed

by Schmidt (1932). Whether his hypothesis be right or wrong, it has no direct bearing on the endocrine function of the carotid gland.

The only conclusion that can be drawn from the work done in this field is that the physiologists have signally failed to demonstrate any specific function of the carotid gland, and this in spite of many clues which can be deduced from the work of the histologists. The intimate association of the carotid gland with the carotid sinus would also suggest some pressor or depressor function.

MATERIAL

To obtain any quantity of pure carotid gland from domestic animals is an almost impossible task. The gland is extremely small, its anatomical relationships are by no means constant, and it is embedded in the dense fibrous tissue surrounding the carotid arteries. Collip and Long (unpublished data) were quite unsuccessful in an attempt to obtain sufficient beef gland for biological assay. Recently we were fortunate enough to obtain a tumor of the carotid gland, which yielded sufficient extract to define at least some of its properties. Details of the case and of the structure of this rare tumor have been published elsewhere (Chase, 1933). Suffice it to say that the structure of the tumor resembled a diffuse hyperplasia, the arrangement of cell islets and capillaries and the morphological character of the cells being comparable to that found in the normal carotid gland.

Within a few minutes of removal from the patient, half of the gland was immersed in pure alcohol, the other half being preserved for histological study. Preparation of the extract was as follows: The gland was thoroughly pulped in pure quartz sand, extracted in the cold with 65 per cent alcohol acidified with acetic acid, and filtered. The alcohol was then evaporated off the filtrate at low temperature and pressure, and the residium diluted with water, 20 parts of this dilution containing the extract from one part by weight of the gland substance. The extract was neutralized immediately before use.

The residue of pulped gland was then extracted with boiling 0.2 per cent HCl, filtered, and neutralized before use. This extract is referred to in the protocols as the "acid extract of the residue."*

EXPERIMENTAL

I. The Virgin Guinea Pig Uterus

With one horn of the virgin guinea pig uterus suspended in Ringer-Locke solution and equipped with the usual bath and lever recording systems, the addition of carotid gland tumor extract to yield a final dilution of 1:2000 invariably initiated rhythmical contractions and an increase of tone in the resting uterus (Fig. I, B). This response was observed five

*We are greatly indebted to Prof. J. B. Collip of the Department of Biochemistry, McGill University for extracting this material and also for his very helpful interest in our work. We are also indebted to Dr. F. A. C. Scrimger, Surgeon, Royal Victoria Hospital, for supplying us with this material.

times on four virgin uterine horns, while control extracts of muscle and brain prepared in the same way produced no stimulation in even 10 times the concentration. The possible relationship of the carotid gland extract to other tissue extracts and to histamine can be dealt with more fully when dealing with the blood pressure response (vide infra).

The acid extract of the residue was without demonstrable effect on the virgin uterus.

At A (Fig. I) an extract from the carotid gland of the sting ray was added. This will be discussed in the second paper of this series and is

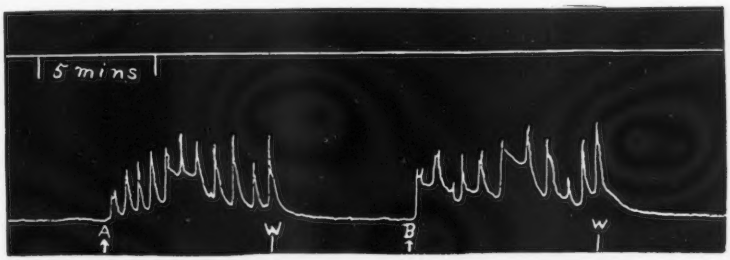

Figure I. Resting virgin guinea-pig uterus suspended in Ringer-Locke solution. A= Addition of sting ray carotid gland extract—dilution 1 :3000. B=Addition of carotid gland tumor extract—dilution 1 :2000. W=Uterus washed with fresh Ringer-Locke solution.

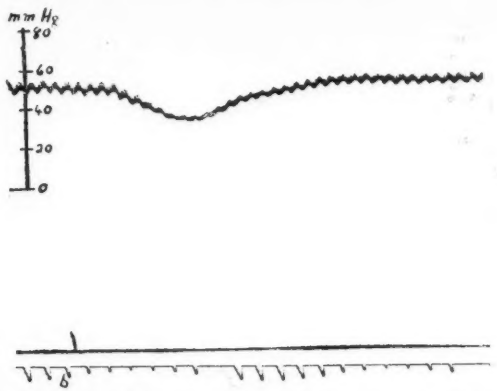

Figure II. Decapitate cat with artificial respiration. 3.0 kgm. Blood pressure tracing. 1 cc. of 1 :20 carotid gland tumor extract intravenously. Time Marker=5 secs.

only inserted here to allow direct comparison of the action of the two extracts on the same preparation.

II. The Blood Pressure

The intravenous administration of the extract from 50 mgm. of gland substance invariably resulted in a transient fall of blood pressure. In the decapitated cat falls of 8 and 14 mm. Hg. were observed (Fig. II); in the decerebrate cat falls of 31, 24, 23 and 38 mm. Hg. were observed

(Fig. III); in two cats under dial anaesthesia falls of 44 and 40 in the one and of 33, 35 and 45 mm. Hg. in the other were observed (Figs. IV and VI); and in a rabbit under dial anaesthesia falls of 17, 8 and 13 mm. Hg. were observed (Fig. VII). The smallness of the blood pressure fall in the

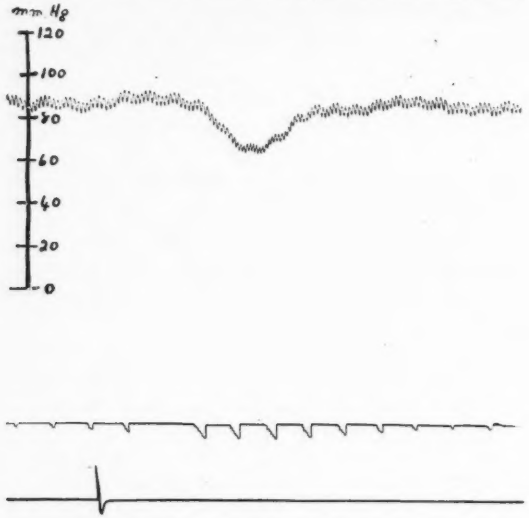

Figure III. Decerebrate cat, 2.80 kgm. Blood pressure tracing. 1 cc. of 1:20 carotid gland tumor extract intravenously. Time Marker=5 secs.

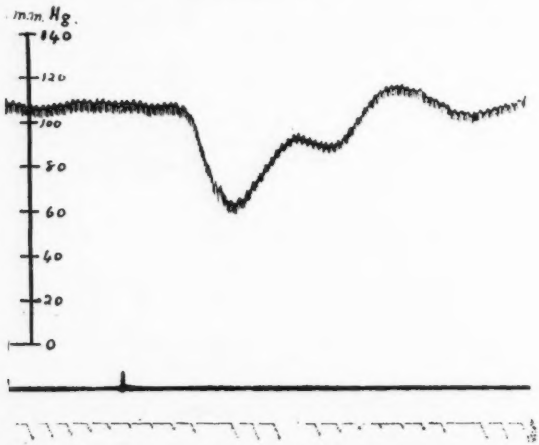

Figure IV. Cat under dial anaesthesia. 3.20 kgm. Blood pressure tracing. 1 cc. of 1:20 carotid gland tumor extract intravenously. Time Marker=5 secs.

decapitated preparation may well be explained by the fact that the initial blood pressure ranged between 50 and 55 mm. Hg., whereas in the other preparations it was never below 80 mm. Hg. and usually above 100 mm. Hg. (Figs. II, III, IV and VI and VII). The diminished response of the

rabbit as compared to the cat cannot be explained on these grounds. To produce a similar rise of blood pressure in the rabbit as in the cat approximately four times the dose of adrenaline is required in the former. If we interpret this as a more sluggish response to vasomotor stimuli in the rabbit, the smaller response to carotid gland extract can be readily understood.

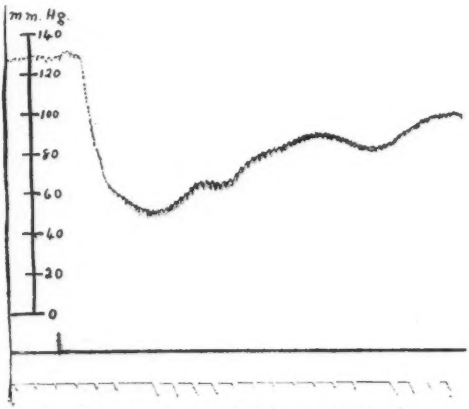

Figure V. Cat under dial anaesthesia. 3.20 kgm. Blood pressure tracing (continuous with Fig. IV). 1/100 mgm. acetyl choline hydrobromide intravenously. Time Marker= 5 secs.

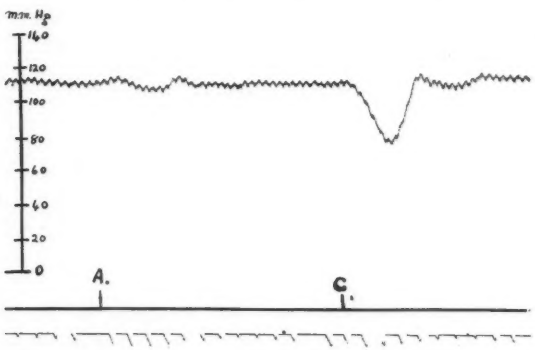

Figure VI. Cat under dial anaesthesia. 3.20 kgm. Blood pressure tracing (continuous with Figs. IV and V), immediately after 1 mgm. of atropine intravenously. A=1/100 mgm. acetyl choline hydrobromide intravenously. C=1 cc. of 1:20 carotid gland tumor extract intravenously. Time Marker=5 secs.

The carotid gland extract evidently contains an active vaso-depressor principle and two possibilities immediately suggest themselves—the presence of acetyl choline or of histamine or of some histamine-like substance.

(a) *Acetyl Choline.* Traces of acetyl choline have been demonstrated in many organs and fortunately its specificity for the vagal nerve endings greatly facilitates its differentiation from other vaso-depressor substances. Its action can be easily abolished by small quantities of atropine. Fig. V shows the fall in blood pressure produced by the intravenous administra-

tion of 1/100 mgm. of acetyl choline hydrobromide to a 3.2 kilo cat under dial anaesthesia. Fig. IV shows the vaso-depressor effect of 50 mgm. of carotid gland on the same cat. After the administration of 1 mgm. of atropine sulphate, the action of acetyl choline is completely abolished, while that of the carotid gland extract remained unimpaired (Fig. VI). A repetition of this experiment yielded exactly similar results.

(b) *Histamine.* Histamine or the histamine-like substances found in certain tissue extracts do not usually yield the regular type of blood pressure curve shown in Figs. II, III, IV, VI and VII. The injection of control extracts of brain, muscle and spleen prepared in the same way pro-

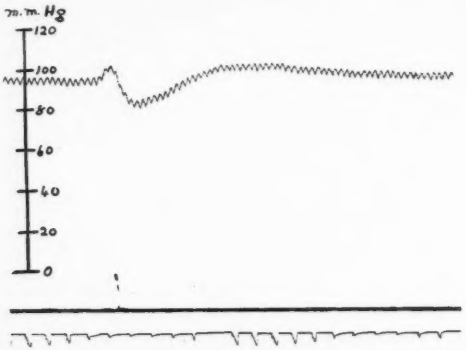

Figure VII. Rabbit under dial anaesthesia. 2.75 kgm. Blood pressure tracing. 1 cc. of 1 :20 carotid gland tumor extract intravenously. Time Marker=5 secs.

duced no fall of blood pressure in even 10 times the concentration. To exclude finally the possibility of some histamine-like substance being responsible for the fall in blood pressure observed with carotid gland extracts, we have used the rabbit which, under certain conditions, responds to histamine by a rise in blood pressure (Feldberg, 1927), the capillaries being relatively insensible to histamine, while the arterioles constrict in the usual manner. A 2.75 kilo rabbit under dial anaesthesia responded to 1 mgm. of histamine by a slight rise in blood pressure (Fig. VIII). A six-months-old extract of spleen known to contain histamine-like substances sufficient to throw the guinea pig uterus into violent contractions produced no significant response in the blood pressure, although 1/10 of the dose given was sufficient to lower the blood pressure of the cat by 18 mm. The carotid gland extract, on the other hand, invariably produced a fall in blood pressure, falls of 17, 8 and 13 mm. Hg. being observed (Fig. VII).

Owing to the limited supply of extract it was impossible to analyze further the site of action of this vaso-depressor substance. We can say with some assurance, however, that its action is peripheral, and is not due to the presence of acetyl choline or any histamine-like substance. It is also thermostable, the acid extract of the residue giving a positive, if diminished, response (Fig. IX).

The Heart Rate. Coincident with the fall in blood pressure an acceleration of the heart rate was constantly observed. In the dial cat a fall of 45 mm. Hg. was accompanied by a cardiac acceleration of 25 per cent; in the decerebrate cat falls of 38, 23 and 31 mm. Hg. were accompanied by cardiac accelerations of 35, 21 and 18 per cent, respectively. The heart rate could not be measured from the tracings in the decapitate preparation.

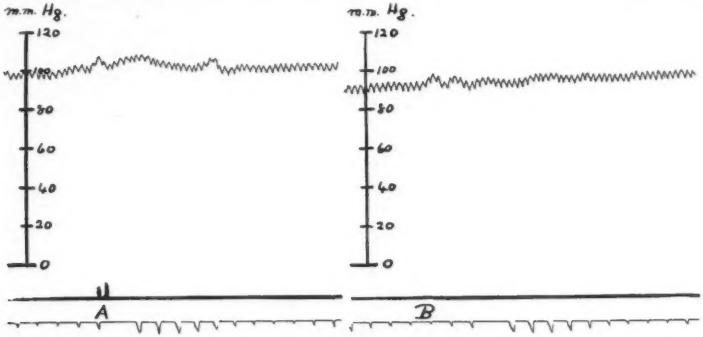

Figure VIII. Rabbit under dial anaesthesia. 2.75 kgm. Blood pressure tracing (continuous with Fig. VII). A=1 mgm. histamine intravenously. B=1 cc. 1:2 extract of spleen intravenously. Time Marker=5 secs.

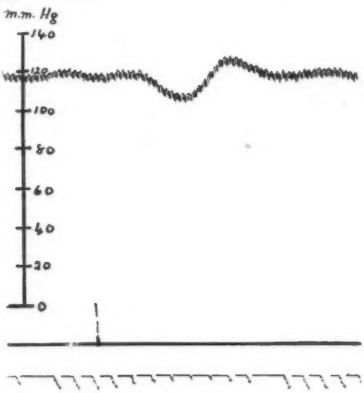

Figure IX. Cat under dial anaesthesia. 3.2 kgm. Blood pressure tracing. 1 cc. of 1:20 acid extract of carotid tumor residue intravenously. Time Marker=5 secs.

Venous Pressure. The intrathoracic venous pressure was measured on one occasion. In the decapitate cat, the fall in blood pressure shown in Fig. II was accompanied by a rise of the venous pressure of 1.8 cm. of H_2O. We are not prepared to discuss the significance of this finding as the time relationships between the rise in venous pressure and fall in arterial pressure were not definitely established.

DISCUSSION

From the mass of evidence which has accumulated as to the innervation and function of the carotid sinus since its discovery by Hering in

1923, and from the evidence as to the innervation of the carotid gland which has been reviewed, certain conjectures can be made. The peculiar types of nerve endings found in the carotid sinus are also found in the carotid gland where they are interposed between the capillary wall and the secretory cell. From these nerve endings in both the carotid gland and sinus, the nerve fibers run direct to the medulla, through the glossopharyngeal and vagus nerves, and are unique in that there are no intermediate ganglion cells. As far as is known, neither the carotid gland nor sinus has any sympathetic innervation. This similarity of innervation from the nerve ending to the medulla itself is certainly suggestive of some similarity of function, and when we consider that stimulation of the nerve endings in the sinus carotidis produces a fall in blood pressure it seems reasonable to suppose that any endocrine function of the carotid gland might also be to lower the blood pressure. This conjecture is certainly supported by the presence of an active vaso-depressor principle in our carotid gland tumor extract. It might well be said that the properties of a tumor may not represent the properties of the parent tissue. However, the morphological resemblance of this tumor to the normal carotid gland has already been emphasized (Chase, 1933), and in tumors of other internal secreting glands, the secretory function persists if there is no reversion to a more primitive type of cell. It might also be said that the presence of a vaso-depressor substance by no means proves an internal secretion. Several vaso-depressor substances have been isolated from tissues in general and something specifically produced by the carotid gland would have first to be proved. (a) Histamine and (b) Acetyl Choline have already been shown to differ from the carotid gland tumor depressor principle. (c) Adenylic acid which occurs mainly in muscle but also in other tissues [Drury and Szent-Györgyi (1929-30), Bennet and Drury (1931), Zipf (1931)], also differs in that it is insoluble in alcohol and produces bradycardia instead of the cardiac acceleration which we constantly observed. (d) The "Kallikrein" of Kraut and Frey [Frey, Kraut and Schultz 1930] is also insoluble in alcohol [v. Euler and Gaddum (1931), Herbig (1932)]. (e) Other unidentified depressor substances occurring mainly in the brain and intestinal mucosa but also in other tissues have been described by v. Euler and Gaddum (1931), Major and Weber (1930), v. Euler (1932), etc. The properties of these substances have not yet been so defined that differentiation from our carotid tumor extract could be attempted. In any case the significance of solubility tests is open to question and the only dogmatic statements we can make are that this carotid gland tumor contains a depressor principle, certain properties of which differ from those of histamine, acetyl choline, adenylic acid and "Kallikrein." Further, the concentration of depressor substance in this extract is many times greater than that found in similar extracts of other tissues. Control extracts of brain, spleen and muscle which should contain these depressor substances in maximal amounts were without effect in even ten

times the dose of carotid gland tumor extract sufficient to produce a profound lowering of the blood pressure. When we consider the structure and innervation of the carotid gland, these findings seem to us to be of significance, the more so since we have been able to demonstrate a similar depressor principle in the carotid gland of the elasmobranch (Christie, 1933). Though realizing the dangers of labeling a vaso-depressor substance as an internal secretion, we would suggest the term Carotidin for this principle.

SUMMARY

Extracts of a carotid gland tumor in man were shown to contain a thermostable vaso-depressor principle in high concentration, which differs in its properties from acetyl choline, adenylic acid, "Kallikrein" or histamine. On the virgin guinea pig uterus, powerful rhythmic contractions were initiated, which also differed in certain respects from those which can be produced by histamine. We have suggested the name Carotidin for this substance. Its action on the blood pressure, the pulse rate, and the virgin uterus is directly opposite to that of adrenaline. The functional relationship of the carotid gland to the parasympathetic nervous system and the carotid sinus is discussed.

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THE FUNCTION OF THE CAROTID GLAND
(GLOMUS CAROTICUM)

II. THE ACTION OF EXTRACTS OF THE CAROTID GLAND OF THE ELASMOBRANCH

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In a previous communication we have shown that an antagonist to adrenaline could be isolated from a tumor of the carotid gland in man (Christie, 1933). We also reviewed the various conceptions of the structure and function of the carotid gland and indicated the unsurmountable difficulties in obtaining any quantity of the gland from domestic animals. In the elasmobranch, however, the gland is of considerable size and can be easily isolated from the surrounding tissues. In the adult sting ray each gland is about 40x5x2 mm. in size, about 20 times larger than in man. It lies in the posterior cardinal sinus and is attached to its posterior wall by only a few strands of fibrous tissue, a few nerve fibers and the axillary artery which runs through its upper pole. The nerve fibers run to the vagus nerve and gastric ganglion which lies medial and in close proximity to the gland. On section the structure of the gland closely simulates that found in the mammal, Leydig, (1851), Schaper (1892), Vincent (1898), Christie and Chase (unpublished). The cell islets, however, do show strongly positive chromaffine reaction. It would be impossible in this species to analyze the nerve supply of the gland, but from its external nervous attachments and the positive chromaffine reaction of its cells, we would suspect it to be supplied by both sympathetic and parasympathetic systems.

It might be said that the presence of a strongly positive chromaffine reaction in the glands of the sting ray and shark and its absence in man would invalidate any supposition of similar function. We admit this. We believe, however, that we can demonstrate the presence of two secretions in the carotid gland of the sting ray and shark; one of which is similar to adrenaline and one which is directly antagonistic to adrenaline and similar to that which we isolated from a tumor of the carotid gland in man (Christie, 1932). The significance of this association of adrenal and carotid gland function is discussed below.

PHYSIOLOGICAL ACTION OF THE EXTRACT

The extract available was confined to the glands of two 10-foot sharks and twenty-four adult sting rays. For this reason we have for the most part confined our experiments to an analysis of its effects on (I) the virgin guinea pig uterus, (II) strips of rabbit intestine, and (III) the blood pressure. The glands were obtained perfectly fresh, in most cases with the heart still beating on removal. It was immediately immersed in pure alcohol and extracted in a manner similar in every respect to that described in the first paper of this series (Christie, 1933).

I. Virgin Guinea Pig Uterus

With one horn of the virgin guinea pig uterus suspended in Ringer-Locke solution and equipped with the usual bath and lever recording system, the addition of small amounts (1 in 3000 solution) of carotid gland extract invariably throws the resting uterus into powerful rhythmic contractions. Usually relaxation is incomplete (Fig. I), but occasionally com-

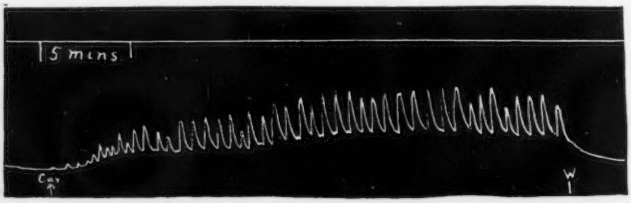


Figure I. Resting virgin guinea-pig uterus suspended in Ringer-Locke solution. Car.= addition of carotid gland extract—dilution 1:3000. W.=uterus washed with fresh Ringer-Locke solution. Time Marker=5 mins.

plete relaxation is observed (Fig. III). In the spontaneously contracting uterus, the addition of carotid gland extract produces an acceleration of contraction and incomplete relaxation (Fig. II). This experiment was

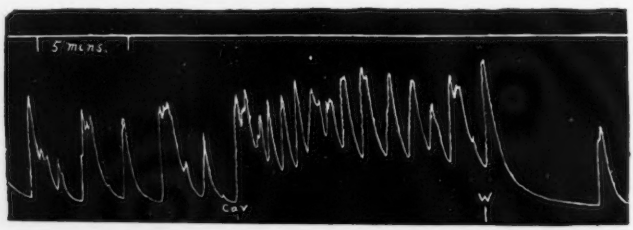


Figure II. Spontaneously contracting virgin guinea-pig uterus suspended in Ringer-Locke solution. Car.=addition of carotid gland extract—dilution 1:3000. W.=uterus washed with fresh Ringer-Locke solution. Time Marker=5 mins.

repeated on 16 occasions on nine virgin uterus horns and one of the types of response described above was invariably observed, a response similar in every respect to that produced by the carotid body tumor extract previously described (Christie, 1933, Fig. I). Acid extracts of the residue produced slight contractions on two occasions, and a negative response on five

(Fig. III). The response to carotid gland extract is entirely different to that observed with pituitrin (Fig. III) and also histamine which gives more irregular spasmodic contractions. Further to exclude the possibility that the reactions observed were due to histamine, we incubated some of the carotid gland extract at room temperature and a pH of 8. After six days this extract could produce only very feeble or no uterine contractions (Fig. II). The active principle is evidently destroyed under these conditions. This pH and temperature are favorable for histamine formation and one would certainly not expect its potency to decrease. Also, control extracts of shark muscle and spleen were devoid of action in even 10 times the concentration of the carotid gland extract. Further evidence for the absence of histamine in this extract is given below. Collip (1920) has shown that tissue extracts may per se stimulate the virgin guinea pig

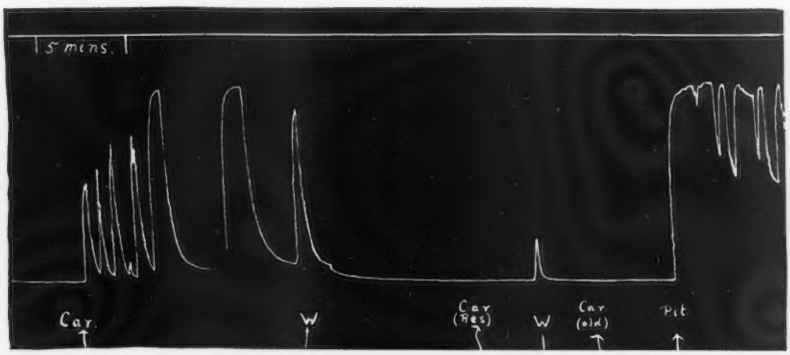


Figure III. Resting virgin guinea-pig uterus suspended in Ringer-Locke solution. Car.= addition of carotid gland extract—dilution 1:3000. Car. (res.)=addition of acid alcohol extract of carotid gland residue—dilution 1:5000. Car. (old)=addition of carotid gland extract kept at pH of 8.0 for 6 days—dilution 1:3000. Pit.=addition of pituitrin—dilution 0.03 units per cent. W.=uterus washed with fresh Ringer-Locke solution. Time Marker=5 mins.

uterus and may antagonize the inhibitory action of adrenalin. It might be said that our carotid gland extracts merely exhibit the properties of ordinary tissue extracts. Against such a supposition are the following points:

(a) Extracts of other organs in as much as 10 times the concentration used with the carotid body extract produces no such stimulation.

(b) Adrenaline in even very low concentrations (1:100,000,000) does inhibit the action of carotid body extract.

(c) As gauged by the blood pressure method of biological assay the concentration of adrenaline in the carotid body extract would give a final dilution in the Ringer-Locke solution of 1:1,000.000. An increase of this concentration to 1.1:1,000,000 invariably gave complete inhibition of uterine contractions—a different picture from that observed by Collip, where four times this concentration of adrenaline was without effect on uterine contractions no more powerful than those obtained by us with carotid gland extract.

The possible relationship of carotid gland extracts to other tissue extracts will be dealt with further when the effects of these extracts on the blood pressure are described (vide infra).

II. Rabbit Intestine

The addition of carotid gland extract produces a definite but transient relaxation of the rhythmically contracting rabbit duodenum (Fig. IV). This reaction is similar to that produced by adrenaline (Fig. IV), a

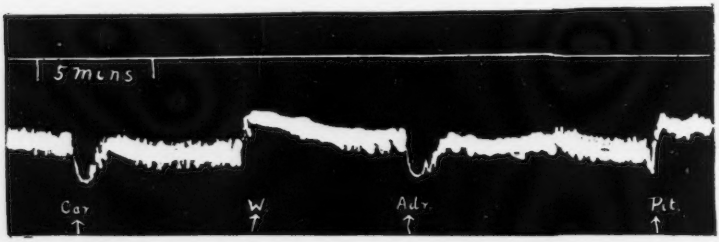


Figure IV. Rabbit duodenum suspended in Ringer-Locke solution. Car.=addition of carotid gland extract—dilution 1:3000. Adr.=addition of adrenalin hydrochloride—dilution 1:10,000,000. Pit.=addition of pitultrin—dilution 2 units per cent. W.=washed with fresh Ringer-Locke solution.

final dilution of 1:3000 carotid gland extract being equivalent to 1:10,000,000 adrenaline. This experiment was repeated eight times with exactly similar results. Other tissue extracts in 10 times this concentration did not affect the intestinal rhythm or tone.

III. The Blood Pressure

(a) *The Presence of a Pressor Principle.* The intravenous administration of extracts of the carotid gland invariably led to a transient rise in blood pressure very similar to that produced by adrenaline. This observation was confirmed on 25 occasions on 11 animals which included cats and rabbits under dial anaesthesia, decapitate cats and decerebrate cats (Figs. VI, VII, X and XIV). The rise in blood pressure in the dial cat was directly proportional to the amount given; 1/3,000 of a gram of gland substance giving a rise of from 13 to 19 mm. Hg.; 1/1200 gm. a rise of from 34 to 35 mm.; 1/600 gm. a rise of from 32 to 46 mm.; 1/300 gm. a rise of from 48 to 61 mm.; 1/60 gm. a rise of from 68 to 116 mm.; and 1/30 gm. a rise of from 79 to 122 mm. Control injections of spleen, muscle, brain and adrenal cortex extracted in a similar manner produced no significant change in the blood pressure with even 10 times the maximum dose of carotid gland extract. When these figures were compared with the effects of adrenaline it was found that a very constant relationship of 1 gm. carotid gland=0.003 gm. adrenaline chloride obtained (Figs. V and VI). The reinforcement of adrenaline by cocaine (Rosenblueth and Schlossberg, 1931), can also be demonstrated with carotid gland extract. The administration of 6 mg. of cocaine hydrochloride intravenously in a decapitate cat increased the rise in blood pressure produced by 1/1200 gm. of carotid

gland from 70 mm. Hg. to 105 mm. Hg. (Figs. VII and VIII). A rise of 47 mm. Hg. produced by 1 cc. 1/400,000 adrenaline was similarly increased to 73 mm. Hg. Ergotamine, on the other hand, greatly diminishes the pressor effect of both adrenaline and carotid gland extract. Rises of 35-41 mm. Hg. produced by 1/400,000 gm. adrenaline chloride and 34-35 mm

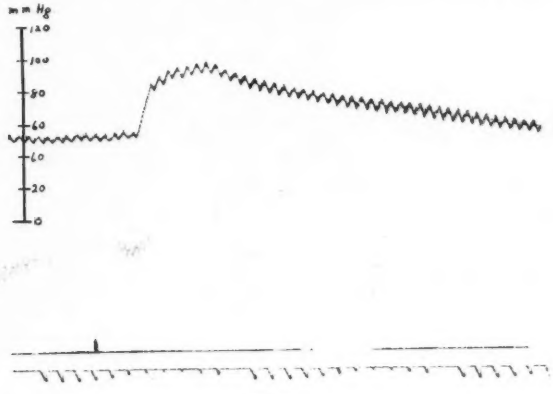


Fig. V

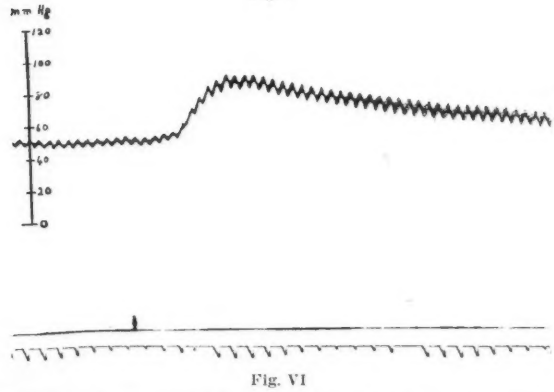


Fig. VI

Decapitate Cat with Artificial Respiration—Blood Pressure Tracing.
Figure V. 1 cc. of 1:100,000 adrenalin hydrochloride intravenously.
Figure VI. 1 cc. of 1:300 carotid gland extract intravenously. Time Marker=5 secs.

Hg. by 1/1200 gm. carotid gland fell to 12-13 mm. Hg. and 14 mm. Hg., respectively, after the administration of 4 mg. ergotamine tartrate to a 3.3 kilogram cat under dial anaesthesia (Fig. IX).

The acid extract of the gland residue demonstrated the same pressor principle but, of course, in much greater dilution, 1 cc. of the acid extract being approximately equivalent to 1/10 cc. of the original carotid gland extract.

It may safely be said from these experiments that the carotid body extract contains a pressor principle which acts through the constrictor

myoneural junctions in a manner indistinguishable from that of adrenaline. The experiments with the virgin uterus, on the other hand, and our previous experience with the extract of a carotid body tumor, would suggest the presence of some substance directly antagonistic to adrenaline. To isolate any depressor from the pressor or adrenaline principle was obviously the next step in our investigation.

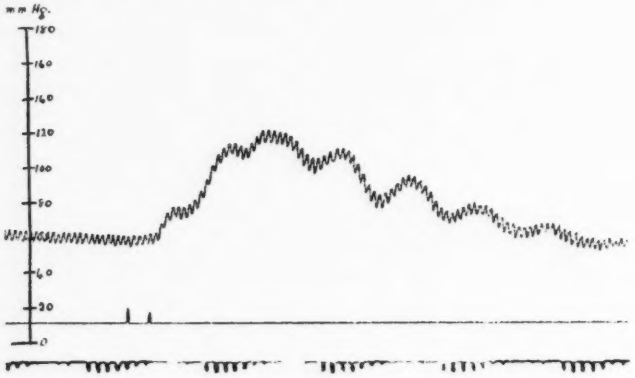


Fig. VII

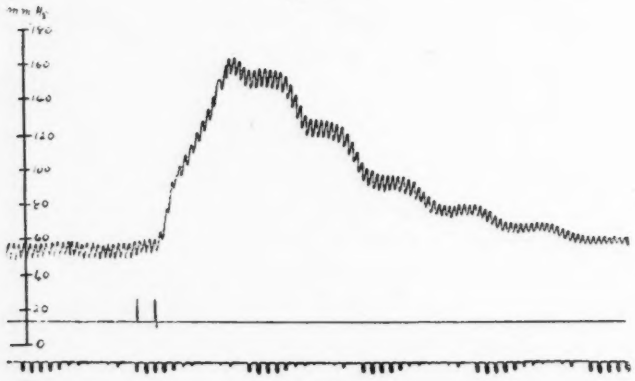


Fig. VIII

Reinforcement with Cocaine. Cat Under Dial Anaesthesia.

Figure VII. Blood pressure tracing before the administration of cocaine—1 cc. 1:1200 carotid gland extract given intravenously between signals.

Figure VIII. Blood pressure tracing after the administration of 6 mgm. cocaine hydrochloride intravenously—1 cc. 1:1200 carotid gland extract given intravenously between signals. Time Marker=5 secs.

(b) *The Presence of a Depressor Principle.* Unfortunately the material at hand was insufficient to destroy any adrenaline by the technic of Swingle and Pfiffner. Instead, we made use of the fact that adrenaline rapidly disintegrates if kept at a pH of 8.0 instead of in the usual acid medium. In the dial cat 1/30 gm. of carotid gland kept for 24 hours in the ice box at a pH of 8.0 was necessary to produce rises of 46, 56 and 38

mm. Hg. in the blood pressure, whereas 1/300 gm. of the freshly neutralized gland was sufficient to produce rises of 48 and 61 mm. If kept for 48 hours in the ice box a similar dose (1/30 gm.) gave rise to somewhat irregular blood pressure tracings, a rise of from 19 to 39 mm. Hg. preceding a fall of from 54 to 122 mm. Hg.

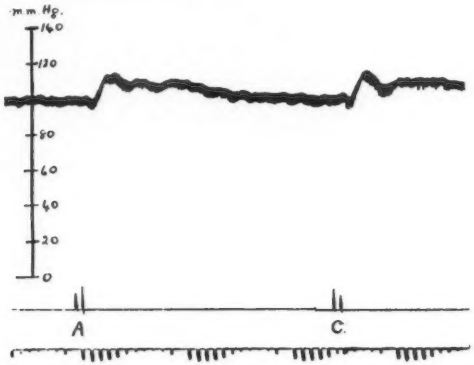


Fig. IX

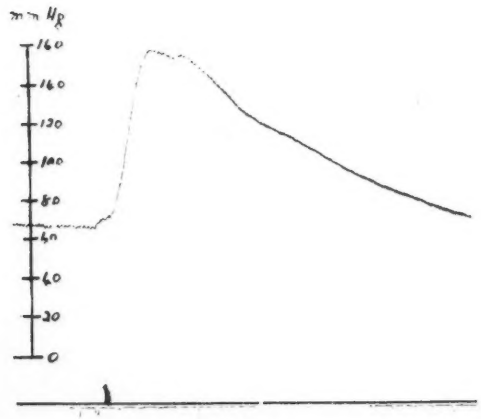


Fig. X

Abolition with Ergotamine

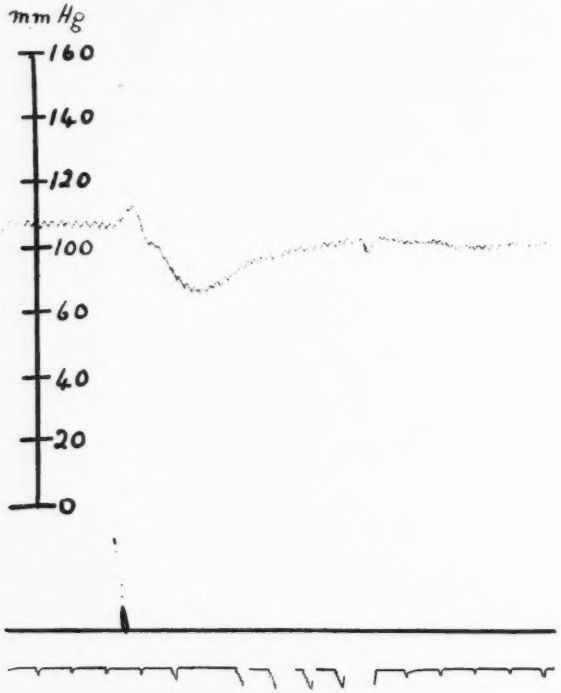
Figure IX. Cat under dial anaesthesia—blood pressure tracing. Sympathetic response partially paralyzed by the intravenous administration of 4 mgm. of ergotamine. A=1 cc. of 1:400,000 adrenalin hydrochloride intravenously. C=1 cc. of 1:1200 carotid gland extract intravenously. Time Marker=5 secs.

Figure X. Rabbit under dial anaesthesia. Blood pressure tracing. Effect of 1 cc. of 1:60 carotid gland extract freshly neutralized. Time Marker=5 secs.

In the rabbit much more clear-cut pressure tracings were obtained. Two rabbits were used under dial anaesthesia. 1/300 gm. of freshly neutralized carotid gland extract was sufficient to raise the blood pressure by 39 and 61 mm. of Hg., and 1/30 gm. sufficient for a rise of 90, 122, 106

and 92 mm. of Hg. (Fig. X). With a similar extract which had been incubated in the ice box for 24 hours after neutralization, 1/300 gm. produced no change in the blood pressure, and 1/30 gm. gave a rise of 18 mm. in one rabbit and falls of 19 and 8 mm. in the other (Fig. XI). When kept at room temperature instead of in the ice box, disintegration of adrenaline was more complete, and falls in blood pressure of 39, 27, 34 and 25 mm. Hg. were observed (Fig. XII).

The obvious criticism of these experiments with an alkaline extract is that the results may have been due to histamine formation which is favored



Rabbit Under Dial Anaesthesia. Blood Pressure Tracings.

Figure XI. 1 cc. of 1:30 carotid gland extract intravenously—neutralized 24 hours previously and kept on ice.

in an alkaline medium. However, no increase of tolerance was shown on successive injections and control extracts of brain and spleen, in even 10 times the concentration and prepared in the same way, produced no fall in blood pressure in either cats or rabbits. Even a spleen extract which had been kept in the alkaline state for over six months and which threw the virgin guinea pig uterus into violent tetanic contracture in dilutions of 1:1000 was without effect on the blood pressure of the rabbit in doses equivalent to ½ gram of splenic tissue (Fig. XIII). The rabbit is extra-

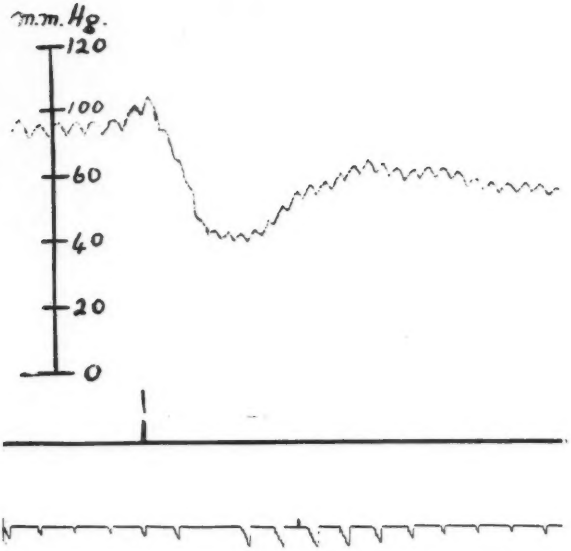


Figure XII. 1 cc. of 1:30 carotid gland extract intravenously—neutralized 24 hours previously and kept at room temperature.

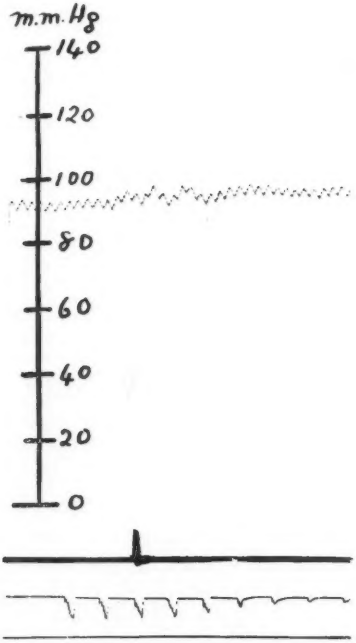


Figure XIII. 1 cc. of 1:2 extract of spleen intravenously—neutralized 6 months previously and kept on ice. Time Marker=5 secs.

ordinarily resistant to the depressor action of histamine, 1 mgm. of pure histamine producing, if anything, a slight rise in blood pressure (Christie, 1933; Feldberg, 1927).

The effects of ergotamine, cocaine and atropin on this depressor principle have not yet been studied owing to lack of material. We believe, however, that we are justified in concluding from these experiments that the carotid gland of the elasmobranch contains an active vaso-depressor substance, which bears no relation to histamine and is presumably similar to the depressor substance which we have isolated from a carotid body tumor in man (Christie, 1933).

IV. The Heart Rate

With the rise in blood pressure produced by the freshly neutralized gland extract, a slowing of the heart rate, similar to that obtained with adrenaline, was usually observed. On one occasion only was there an acceleration of the heart rate and this occurred on the injection of a large dose of the extract (1/30 gm. of gland substance). In this experiment a rise of 72 mm. in the blood pressure was accompanied by an increase of the heart rate from 94 to 196 per minute. This acceleration may or may not have been due to the depressor principle whose action on the heart rate we have not yet been able to analyze owing to lack of material.

V. Venous Pressure and Respiration

Respiratory and venous pressure tracings showed that the freshly neutralized extract of the carotid gland may produce a transient apnoea and rise in venous pressure similar to that observed with adrenaline.

DISCUSSION

It is evident that the carotid gland of the elasmobranch contains both adrenaline and an antagonist to adrenaline. This antagonist is indistinguishable from that which we isolated from a carotid gland tumor in man, and for which we suggested the term Carotidin.

From a morphological and embryological point of view there is little difference between the sympathetic and parasympathetic tissues, although functionally they may be directly antagonistic. Similarly the carotid gland and adrenal medulla are closely related from an embryological point of view and a certain resemblance in their morphological structure is by no means indicative of similarity in function. Thus the similarity of the morphological picture of the small basophilic (sympathogonic) cells in rosette arrangement in human carotid body tumors to the cells of the so-called "neurocytoma" and "neuroblastoma" of the adrenal medulla has been repeatedly noted. Also Chase (1933) has observed occasional chromaffine cells in the carotid gland of man but was unable to obtain any positive tests for adrenaline. He states, "It may be that the material which gives the chrome reaction in the carotid bodies is either an adre-

naline building substance or a substance closely related to adrenaline which does not give its specific histo-chemical reactions." De Castro (1927-28) was occasionally able to find a chromaffine cell in the carotid gland of the cat without any positive reactions for adrenaline. De Castro (1926) has also shown that in contradistinction to man, the glands of dogs, cats and to a lesser extent mice, are surrounded by a dense plexus rich in sympathetic fibers, some of which actually penetrate the gland, although they do not innervate the secretory cells. This relationship of the mammalian carotid gland to the sympathetic system and adrenal medulla, closer in the lower mammals than in man, makes the intimate association of the adrenal medulla and carotid gland in the elasmobranch more easily understood. In the sting ray the anatomical association of the carotid gland and adrenal medulla is evidently complete, no medullary substance being found outside the posterior cardinal sinus. The adrenal cortex of the sting ray lies as a discrete gland behind a kidney, and contains no adrenaline or vaso-pressor substance. In the shark the cortex lies scattered behind the kidney in intimate contact with portions of medullary tissue. More medullary tissue is found scattered along the sympathetic chain and in the posterior cardinal sinus where it is incorporated in the carotid gland.

It is interesting that the relative potencies of the pressor and depressor fractions of this carotid gland extract vary with the type of cell or nerve ending upon which they act. On the virgin uterus it is the vaso-depressor which is dominant, while on the blood pressure this is overshadowed by the pressor response to adrenaline. The intestine apparently occupies a somewhat intermediate position.

The site of action of this vaso-depressor, its relationship to other sympathetic phenomena and to carbohydrate metabolism, have not yet been investigated owing to lack of material.

SUMMARY

The carotid gland of the elasmobranch has been shown to contain two active principles. The one, a vaso-pressor principle acting on the constrictor myo-neural junctions is indistinguishable from adrenaline. The other, a vaso-depressor principle, for which we have suggested the name Carotidin, is similar to that which we isolated from a human carotid gland tumor, both in its action on the blood pressure and on the virgin guinea pig uterus.

We wish to thank Dr. A. L. Loomis of the Loomis Laboratories, Tuxedo Park, New York, for making this investigation possible and for his personal co-operation in securing the necessary material.

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THE EFFECT OF EARLY GONADECTOMY ON THE GROSS BODY ACTIVITY OF RATS

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The relation between the normal level of spontaneous activity in rats and the function of the sex glands has been demonstrated in several experiments. Wang ('23) found the running activity of adult females in revolving drums to be reduced as much as 95 per cent by removal of the ovaries. Hoskins ('25) found that removal of the testes in adult males had a similar depressive effect. In keeping with these observations made on adults, it was found further that rats spayed or castrated before puberty, from 28-40 days of age, showed a constant low level of activity throughout life which averaged less than 2,000 revolutions per day. (Wang, Richter and Guttmacher, '25; Richter and Wislocki, '28.) That the sluggishness of these gonadectomized animals was due to the absence of the sex glands was demonstrated by replacement therapy which consisted of the implantation of the sex glands or the injection of their extracts. Successful implantation of ovaries into rats castrated or spayed before puberty caused an increase of activity from 1,000 revolutions per day to the normal average of 10,000 (Wang, Richter and Guttmacher, '25). Subsequent removal of these grafts had the same effect as spaying in normal adult females, the activity dropping almost immediately to the permanent low level. Injection of follicular extracts into spayed females raised the activity to the normal average (Bugbee and Simond, '26; Wang and Richter, unpublished), and implantation of testes into males castrated before puberty produced a less marked but similar effect (Richter and Wislocki, '28).

All these experiments establish quite clearly the dependence of spontaneous activity on the presence of gonads in young as well as in adult animals. However, since Gans ('27) reported that animals castrated at the early age of 1-10 days became just as active as normal controls, the castration experiments have been repeated in both males and females of 1-10 days of age. The results of these experiments are reported below.

METHODS

Our technique of measuring activity has been described in detail in previous papers (Richter, '27). It is sufficient to state that daily records were made of the activity, food and water intake, and weekly readings of the body-weight.

Fifteen rats, eight males and seven females from four different litters, were castrated and spayed at varying ages, from 1-10 days after birth.

They were permitted to stay with their mothers until the thirty-fifth day, at which time they were placed in the activity cages.

For purposes of comparison, averages were computed from the records of nineteen normal males and nineteen normal females.

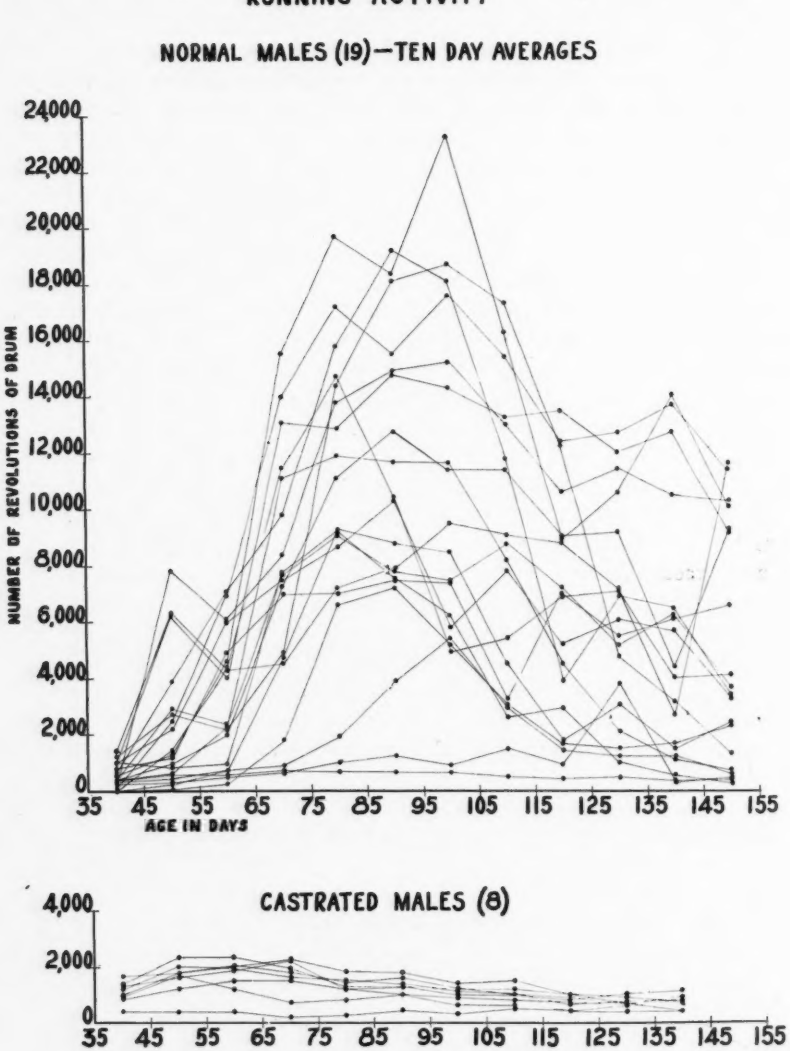

Figure 1. Top—Ten day averages of running activity of 19 normal male rats. Ordinates: number of revolutions of drum per 24 hours. Abscissae: age of animals in days.
Bottom—Ten day averages for eight males, castrated 1-10 days of age.

RESULTS

The effects produced by early castration on the activity of eight males may be brought out by comparing their daily charts with those obtained from nineteen normal males. In the accompanying graphs (Fig. 1) the

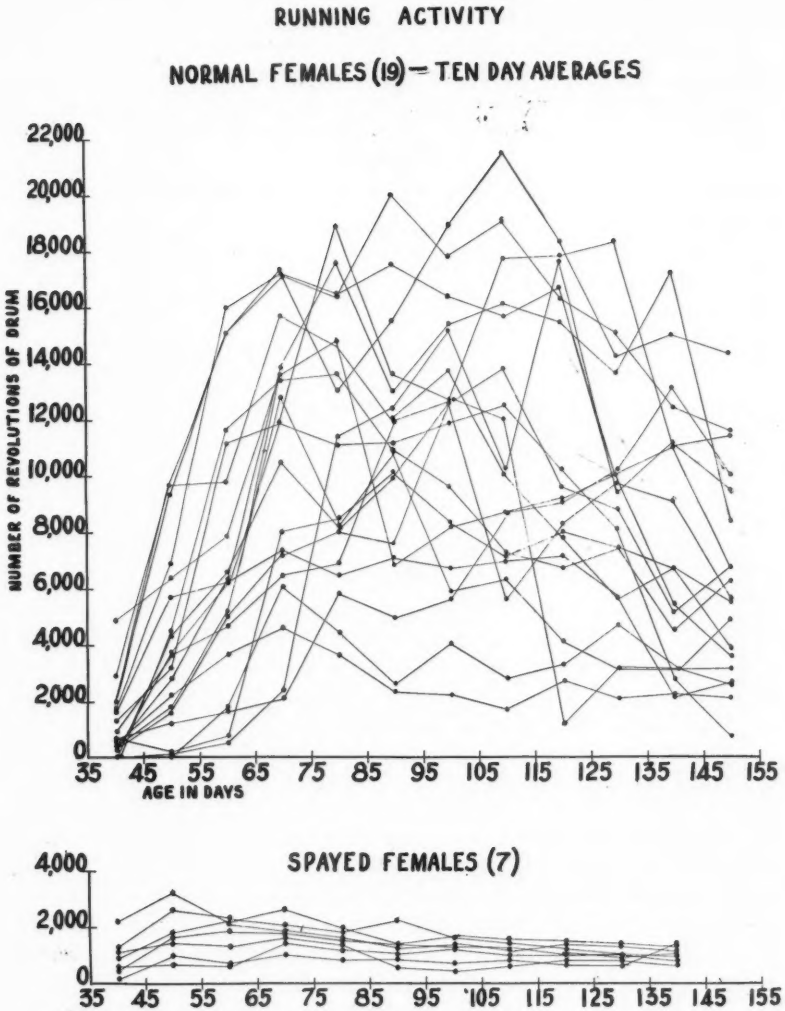

Figure 2. Top—Ten day averages of running activity of 19 normal females. Bottom—Ten day averages of seven females spayed 1-10 days of age.

activity measured in revolutions of the drum is indicated on the ordinates, the duration of the experiment in days on the abscissae. The individual curves (plotted from ten-day averages) for the normal males are shown

above, the curves for the castrated animals below. The controls show a wide range of variation in activity, from a level of only a few hundred revolutions per day to over 23,000. However, they have in common a short period of inactivity for the first 10-20 days in the cages, then a rapid increase to a plateau (in many instances over 10,000 revolutions daily) and finally a gradual decrease.

The difference between the activity curves of these normal animals and those of the castrates is very striking. The curves of the latter, to be sure, all show a rise of activity during the first ten days, a plateau, and finally a

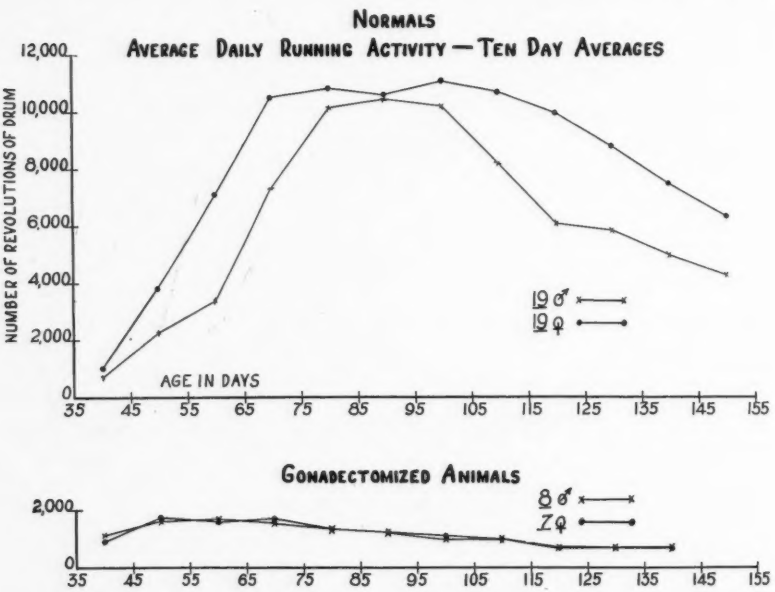

Figure 3. Top—Ten day averages of running activity of 19 normal males and 19 normal females.
Bottom—Ten day averages of 8 castrated males and 7 spayed females.

gradual decrease. However, none of the castrated animals made over 2,200 revolutions per day and few of them made much less than 2,000. They follow one another so closely that with the exception of one animal, a statistical treatment becomes unnecessary.

The effect produced on the females by early spaying may be seen in Fig. 2. The change here is practically identical with that produced in the males. The animals were fairly sluggish, their activity averaging little more than 2,000 revolutions daily. Their curves are practically identical, eliminating the wide range of variation observed in normals.

A comparison of the effect produced on males and females by early gonadectomy can be made in Fig. 3, which gives the averages for both sexes of normal and operated animals. The curves show that during the

period of maximum activity the normals were about five times as active as the gonadectomized animals. Moreover, the normal females were somewhat more active than the males throughout the time of the experiment, the plateau of activity reaching a level of 10,500 daily revolutions in the females, and 10,000 in the males. In contrast, the operated males and females with a plateau near 2,000 revolutions per day show no sex differences at all.

These results in general agree with the observations made on animals gonadectomized at slightly greater ages of 24-40 days. It is true, however, that animals gonadectomized at very early ages do seem to be somewhat more active than those castrated a little later and much more active than animals castrated after maturity. This is an unexpected result inasmuch as the effects on sex activity are just the reverse; animals castrated before puberty never show any sex activity, while animals castrated after puberty may show subsequent sex interest for a surprisingly long period (Stone, '27).

These observations differ very widely from those reported by Gans ('27) who, as was mentioned above, found that animals castrated at ages of 1-10 days were as active, or even more active than the normals. His normal and castrated rats reached a plateau near 4,600 revolutions per day as compared to our level of 2,200 revolutions for the castrates, and 10,000 revolutions for the normals. Thus his castrates showed a higher number of revolutions than ours, and our normals a much higher level than his. The difference in the levels of the castrates may be partly due to the smaller cages used by Gans, which were only 12 inches in diameter as compared to our drums of 13-inch diameter, so that one revolution of his drum represents a shorter distance than one revolution of our drum. It may also be that at the early ages the rats are able to spin a smaller drum more readily than the larger drum. In any case, Gans' castrated rats were not much more active than our castrates. Our normals, however, were very much more active than his normals, especially when the difference in the size of the drum is taken into account (10,000 revolutions per day as compared to 4,500 revolutions). Gans' normals were not as active as most animals described in other papers from the same laboratory. The conclusion must be drawn that his normal animals either were not in a perfect condition or that they were subject to some disturbance which had a pronounced inhibitory effect on their activity. Our experience has been that the activity of normal males can be disturbed more readily than that of the females by change of diet, disturbance in the cage, etc.

DISCUSSION

The above experiments have shown that removal of the sex glands produces a decrease of about 4/5 in the daily running activity of the rat. This does not mean that the amount of activity lost was produced by the sex glands alone, or that it served as a substitute for sex activity. From

the results of other experiments it has been learned that the activity level can be reduced almost as much by thyroidectomy, and much more by adrenalectomy and hypophysectomy. It would follow, then, that this high running level is dependent in some way on the presence of secretory products, at least, of all four glands.

The factors involved in the maintenance of the degree of activity remaining after gonadectomy are unknown. It is clearly not related to search for food or water, since these are provided at all times, and search for an outlet for sex activity can be entirely eliminated. It may be that the other glands, the adrenal and pituitary are responsible for it directly and the higher normal level may represent an integrative effect dependent on the proper interrelationship of all the endocrines and their hormones.

Although the mechanism involved in the reduction of activity is not clear, the fact that gonadectomized animals give such constant curves with a relatively low level and with very small individual variations establishes their usefulness as baseline material for testing the efficacy of replacement therapy, either by implantation or by injection of glandular extracts.

SUMMARY

1. Fifteen rats, eight males and seven females, gonadectomized 1-10 days after birth, were much less active (running activity measured in revolving drums) than normal animals.

2. The normal females reached a plateau at 120 days near 10,500 revolutions, the males near 10,000.

3. The gonadectomized animals reached a plateau at 50 days near 2,000 revolutions. Their greatest activity was less than one-fifth that of the normals.

4. In contrast to the normal males and females, which showed wide individual differences in activity, with levels ranging from a few hundred to over 23,000 revolutions daily, the gonadectomized animals showed no differences at all.

5. Gonadectomy completely eliminated all sex differences in activity. The castrated males and females were equally active at every age, with curves so parallel as to be almost indistinguishable.

6. The great consistency and the constant low level of the activity curves obtained from gonadectomized animals suggests their usefulness in testing various methods of replacement therapy either by implantation of glands or by injection of glandular extracts.

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BOOK REVIEWS

LECTURES ON ENDOCINOLOGY. W. Timme. Paul B. Hoeber, Inc., New York. 2nd Ed., 1932.

The text bears out the statement of the author in the preface to this new edition that the material was chosen "for easy and rapid reading." According to the publisher, "It is written in a clear and succinct manner. The technical details are described in such a fascinating style that it reads like a novel. It is scientific, concise and comprehensive, safe and sane, accurate and authoritative, and exceedingly practical." With the first half of the quotation the reviewer is in substantial agreement. Otherwise the book is interesting mostly as an exposition of the author's empirical credo that has been evolved from a broad experience that differs in various fundamental respects from that of most other students in this field.

A large proportion of the fundamentally important recent advancement of endocrinology is necessarily excluded from a book of this brief scope.

HUMAN HEREDITY. E. Baur, E. Fischer and F. Lenz. Translated by E. and C. Paul. The Macmillan Company, New York, 1931.

This book is of relatively slight immediate interest to endocrinologists in that only a few hormonal disorders are considered. These include gigantism, dwarfism, hyperthyroidism, cretinism, diabetes mellitus and diabetes insipidus. The space accorded to these disorders amounts to only a dozen or two pages, all told. Rather is it of interest to the student who would acquire a background for the study of these and other endocrinopathies. The endocrinology, as such, is rather elementary. The remarkable statement is made that endemic hypothyroidism can be correlated with admixture of Mongolian blood in the inhabitants of the affected regions.

The book is divided into five sections. The first—and most adequate—is devoted to a survey of the general theory of variation and heredity. The second discusses these matters particularly in relation to the human species. The third section deals with the chief hereditary diseases and anomalies; the fourth with methods for the study of human heredity. The fifth section is devoted to the inheritance of intellectual gifts.

The text is delightfully readable and the illustrations numerous and informative.

THE ORGANS OF INTERNAL SECRETION. I. G. Cobb. William Wood & Co., Baltimore. 4th Ed., 1933.

This book might be not inaptly retitled, "Endocrinology in Fourteen Easy Lessons." It is a curious mélange of some of the best and some of the worst in current endocrinology. No small proportion of the information set forth is frankly quoted from a commercial source. The revision

that, according to the preface, the work has undergone amounts to little more than addition of random scraps of information from recent papers. Some readers will like the book for its readability and enthusiasm.

LES PROBLEME DES GLANDES A SECRETION INTERNE. LES PROPRIETES PHYSICO-CHIMIQUES ET PHARMACODYNAMIQUES DES HORMONES. II. LA THYROIDE. L. Blanchard, H. Penau and H. Simonnet. Les Presses Universitaires de France, Paris, 1932. Pp. 400.

Rarely does a book come to the attention of the reviewer which so neatly fulfills the hopes aroused by its title as does this monograph. It is a model of logical arrangement with instructive and comprehensible illustrations and skillful use of tabular material rapidly to set forward the thought.

After brief but comprehensively epitomizing chapters on thyroid morphology and physiology the authors get at their thesis, proper. Some of the chapter headings are: Chemical Composition of the Thyroid; Concentration and Isolation of the Active Substance (with "flow sheets" of the principal investigators in this field); Properties of Thyroid Derivatives. Then the pharmacodynamics of thyroid substance is treated in detail; some of the topics dealt with are: toxicity; effects on development of higher animals and on growth and metamorphosis of lower forms; effects on unicellular organisms and tissue cultures. Then follows a discussion of the relation of the thyroid to various sorts of metabolic and physiological activities.

The book closes with a 67-page bibliography bringing the literature up to 1930—but adding a few more recent titles regarded as of special interest. This list as well as the text betokens familiarity with the literature of the world. The reviewer was unable to think of any important article that, upon checking, was not found in the list.

The book is commended in highest terms to those who desire quick orientation in the field covered or who have occasion to use a reference work to "run down" technical details. It should be in the library of every specialist in endocrinology.

SIMPLIFIED DIABETIC MANAGEMENT. J. T. Beardwood and H. T. Kelly. J. B. Lippincott Co., Phila., 1931. Pp. 191.

The book is addressed both to the victim of diabetes and to the non-specialized physician who has an occasional diabetic to deal with. An attempt has been made—and with apparent success—to include the practical information necessary to the purpose suggested in the title. The text is clear and as free as the subject permits of confusing technicalities. Perhaps the most noteworthy feature is a chart showing the recommended "C-P-F" proportions for diets ranging from 900 to 2800 calories daily. This is an adaptation of Lawrence's "Line ration scheme." Its use is explained in some detail in Chapter II. "It is believed," say the authors, "that this is the first time a complete scheme of this type has been presented."

THE DIFFERENTIAL DIAGNOSIS OF ENDOCRINE DISORDERS. A. W. Rowe. The Williams and Wilkins Company, Baltimore, 1932. Pp. 220.

This book finds its major significance as an exposition of the philosophy of endocrine diagnosis. It is based on an experience of the author and his colleagues in twenty years of intensive study of some five thousand patients. The first step in the development of Rowe's method was the systematic application of a "long series" of vital function tests to normal subjects under carefully controlled conditions whereby the "individual level of performance" could be exactly determined. "Tests were retained or discarded as they served or failed to define standards of normality within their reasonable limits of variation." The next step was the application of the same series of tests to subjects exhibiting clean-cut uniglandular endocrinopathies. There came thus to be recognized deviations from metabolic normality characteristic of each gland disorder. In almost no instance were anything like pathognomonic individual tests found; the exceptions, and these were relative, were very low oxygen consumption rates in high grades of thyroid deficiency and notably high galactose tolerance and high blood uric acid level in similar pituitary deficiency. In general, the different hormone deficiencies were characterized by definitive combinations of abnormal reactions. Upon this relatively simple basis the diagnostic system was built up.

The simplicity in principle, however, was found to involve a high degree of complexity in practice. Each individual finding had to be separately evaluated in relation to intercurrent non-endocrine diseases, and allowance commonly had to be made for such intrinsic variables as age, sex, state of nutrition, and personal habits. Having appraised the influence of each of these variables on the given test finding or observation, the quantitative value of the deviation was next considered as an index of severity of the endocrinopathy.

During the course of the twenty years various new tests have been added to the armamentarium and the results of each integrated with the accumulated results of other tests. The result is a complexity of interrelationships that makes demands upon the "apperceptive mass" of the author that he probably does not realize.

Chapter I of the book is devoted to a discussion of the principles involved. Chapter II is especially valuable as setting forth the practical routine that permits the collection of the mass of material utilized in the diagnosis. In addition to the testing, proper, a detailed case history is obtained and a complete general physical examination is made. Based on the latter, further examinations are scheduled for consultant specialists as needed.

The remainder of the book is largely made up of an analysis of 500 cases diagnosed by the author as "pituitary," "thyroid," or other gland involvement, together with interwoven pertinent discussion. Being itself in the nature of a summary the work cannot be adequately epitomized. It demands careful study, even by the specialist in this field.

The book does not lend itself to critical appraisal. Its significance rests to a considerable extent on the validity of the diagnoses recorded and the data for independent judgment on these have not been presented. The distributions of the test findings in neither the normal controls nor the standard endocrinopathic subjects are given nor is the number of either stated. Thus the statistical validity of the work is left indeterminate.

While the Director of a busy diagnostic clinic presumably has but scant inclination and certainly has little time for these hum-drum details it is to be hoped that he will place his fellow-endocrinologists under further obligations by publishing them.

Despite these obvious faults of omission the work is of outstanding importance as a paradigm. It points the most promising and probably, in principle, the only way by which the multifarious difficulties of endocrine diagnosis can ever be conquered.

ABSTRACTS

Studies on the physiology of reproduction; the adrenal cortex in pregnancy and lactation. Andersen, Dorothy H. and H. S. Kennedy, J. Physiol. **77**: 159. 1933.

A survey of the literature left the authors in doubt as to whether hypertrophy of the adrenals occurs in pregnancy. This paper is a report of an investigation of this point in rats. Animals were mated for one night during oestrus. They were killed in groups on the tenth, eighteenth and twenty-first days of pregnancy; during parturition; and on the first, seventh, fourteenth and twenty-first days of lactation. There were 20 pregnant and 21 lactating animals. Controls were taken from a series previously reported. There was also a series of 41 rats that became infected and 4 pseudo-pregnant rats. There was no hypertrophy during pregnancy nor in pseudo-pregnancy. The figures correspond to those for dioestrus, and are less than those of normal non-pregnant rats during oestrus. During lactation there was a significant increase in weight of the adrenals. In all moderately or severely infected animals the weights were greater.—C. I. R.

Effects of administration of cortical adrenal extract to the hypophysectomized anuran. Atwell, W. J., Proc. Soc. Exper. Biol. & Med. **29**: 621. 1932.

Larvae of Rana sylvatica were hypophysectomized at the tail-bud stage. At different ages thereafter groups of animals were given cortical adrenal extract by intraperitoneal injection. Female animals treated for a period of about 2 months beginning at 5 months of age showed a definite stimulation of the ovaries. Younger animals treated for periods of 2 or 3 weeks did not exhibit this effect. The ovaries of treated animals averaged 2½ times the size of those from hypophysectomized untreated controls. Histologically, untreated animals showed ovaries with large ovocytes in the central part of the gland but with much interstitial tissue and a cortex which appeared to be relatively quiescent in that it consisted of many ovogonia and only small numbers of ovocytes. The ovaries of treated animals, on the other hand, were distended with many large ovocytes located in the cortex as well as centrally. The interstitial tissue and the residual nests of ovogonia in the cortex were reduced to relative insignificance. The whole histological picture was that of recent enlargement of numerous ovocytes in the cortex of the gland. The adrenal seemed to be somewhat restored by administration of cortical extract in that the cortical cells seemed larger, and definitely to contain more lipoid material as shown by treatment with osmic acid. The medullary cells in the treated animals constituted a smaller proportion of the gland. Whether this was relative only, due to enlargement of the cortical cells or to actual reduction of the size of the medullary cells has not been determined. There was no effect on pigmentation, growth, differentiation or upon the thyroid gland.
—M. O. L.

The origin of glucose liberated by epinephrine in depancreatized animals. Bollman, J. L., F. C. Mann and C. M. Wilhelmj, J. Biol. Chem. **93**: 83. 1931.

Depancreatized animals were maintained in good condition by large doses of insulin and appropriate feeding. Four days after the withdrawal of insulin, epinephrine increased the glycosuria beyond that which could be acounted for by the conversion of protein to glucose. At the end of a 12 hour period of administration of epinephrine there was little change in the glycogen or glucose content of the liver. The glucose content of the blood and muscles was not materially altered. There was a marked decrease in the glycogen content of the muscles, which in these experiments was reduced to very low values (20 to 30 mg. for each 100 gm. of muscle). In all experiments the glucose found in excess of the ratio between the dextrose and the nitrogen of 2.8 was almost identical in amount with the loss of glycogen from the muscle. Evidence of formation of glucose from other substances (fat) was not obtained.—Authors' Summary.

Hypertension, obesity, virilism and pseudohermaphroditism, as caused by suprarenal tumors. Cecil, H. L., J. A. M. A. **100:** 463. 1933. Abst., A. M. A.

The author believes that pheochromocytomas cause paroxysmal hypertension by producing large amounts of epinephrine and suddenly releasing it into the blood stream. They sometimes produce a constant hypertension. Neither atrophy nor absence of the opposite suprarenal has been found associated with these tumors. Hypertension is also caused by cortical tumors with a return to the normal after removal of the tumor. In pseudohermaphroditism of the congenital type, removal of one suprarenal, even when it was enlarged has had no beneficial effect on the anomaly. Much can be done by plastic surgery and the persons restored to something approaching normal. The sex should be determined and the anomaly corrected in accordance. The opposite has been done with poor results. In pseudohermaphroditism of the acquired variety, removal of the tumor or of one suprarenal, in cases of hyperplasia, has been followed by gratifying results with the return to the normal state or nearly so. There are great variations in the type change and the degree. In boys the change is toward the adult. In girls and women the change is toward the adult male type. After puberty in males and after the menopause there is no change noted. The author cites two unusual exceptions which lead one to believe that the sex change were brought about by an indirect action of the suprarenal through the ovaries. The author's review of the reported cases shows conclusively that the suprarenal opposite the tumor atrophies and is not congenitally absent. All degrees of atrophy from a slight beginning to total absence have been observed. This important point has not been previously noted. It is of the greatest importance, as removal of one suprarenal cannot ever be done with safety without determining the condition of the other. The symptoms of suprarenal cortical tumors are variable, depending on the sex, the time of onset, and the rapidity of the growth. Two syndromes have been described: (1) the obese type, occurring in female children and adults; (2) the herculean type, occurring in male children and adolescents. These two types are fairly characteristic of suprarenal cortical tumors.

The influence of cortico-adrenal extract on energy output. Eagle, E., S. W. Britton and R. Kline. Am. J. Physiol. **102:** 707. 1932.

The influence of cortico-adrenal extract on the energy output of dogs running in a treadmill has been studied. Three animals were observed for periods of four, five and seven months. After the standard running capacity had been established, the effects of adrenal extract were tested. Intraperitoneal injection of the extract was found to augment markedly the energy output up to 100% or more above the normal. The average increase in six series of experiments was 90%. The running time and the distance run were increased about 90%. In one instance an animal which regularly ran a distance of about 4 miles before treatment covered over 9 miles under the influence of cortico-adrenal extract. The effects were noticeable for 10 to 15 days after injection. Blood sugar almost invariably fell during prolonged running and its course was not notably altered by cortico-adrenal extract.

—Authors' Summary.

Further studies on the action of the suprarenal cortical hormone. Harrop, G. A., Jr. and A. Weinstein, Tr. A. Am. Physicans, **47:** 274. 1932.

During the past two years the authors have treated nine cases of Addison's disease with suprarenal cortical extract made according to the Swingle Pfiffner method. No toxic effects have been observed either on animals or in the clinic as a result of many hundreds of injections. However, unskilful or careless preparation of the material may result in a toxic product. During the past three months the authors have been using extracts prepared from whole beef suprarenal gland which has from 10 to 20 times the potency of the extracts as originally prepared from dissected cortex alone. Nine cases of Addison's disease have been treated with the cortical extract obtained from cortical tissue alone for periods varying from 3 to 18 months. There have been five deaths, four showing at autopsy marked or complete cortical atrophy, and one bilateral suprarenal tuberculosis. Four patients are living, three in good condition with somewhat restricted activity. The results indicate a more favorable

effect in patients treated early in the disease and in those who have had few or no relapses. There is, in general, absence of striking effect on weight and blood pressure. Further experience confirms the fact of the bad effect of measures which raise metabolism, such as fever, thyroid extract, or exhausting exercise, and the authors stress the importance of accessory therapeutic measures such as rest, warmth, fluids, and the use of glucose. Aside from the usual signs and symptoms of the disease, increased sensitiveness to minute intravenous injections of insulin, and the characteristic postural changes in blood pressure are of assistance in the diagnosis of early cases. The changes due to suprarenal insufficiency produced by extract withdrawal in suprarenalectomized dogs are well defined. They consist of anorexia, loss of weight, nutritional disturbances, lowering of body temperature, frequently bradycardia, profound muscle weakness and often terminally vomiting and diarrhea suggestive of a toxic process. During this period there is a marked drop in respiratory metabolism. This factor of adrenal insufficiency parallels the relapse in Addison's disease rather closely, the most striking difference being the absence of pigmentary changes. The effects of cortical hormone injections, even of massive doses, on the respiratory metabolism of the intact or suprarenalectomized animal already adequately treated with extract are practically nil. There is sometimes a tendency to lowered metabolism with adequate extract treatment after suprarenalectomy, but there is a 20 to 30% lowering during insufficiency due to extract withdrawal. When extract is resumed, and the insufficiency is relieved, the metabolism returns to normal. At no period is the basal metabolism increased above the normal level by use of the extract. There are no effects whatever to be observed as a result of overdosage. The minimal maintenance extract requirement varies with metabolic activity. Factors which increase metabolism—fever, exposure to cold, exercise, and the injection of thyroid extract—increase the extract requirement or induce insufficiency. The extract requirement appears considerably higher in the growing animal than it is in the adult. A condition which increases the maintenance requirement, contrary to what might be expected in view of the lowered metabolism, is that of marked undernutrition or cachexia, often shown during recovery from distemper or any acute infection. The nutritional disturbance resembles that of a vitamin deficiency and animals may die in spite of administration of large amounts of extract. Anorexia may be prolonged and exceedingly difficult to overcome, while the animals lose all or most of their surplus body fat.—I. B.

The effect of cortin in asthenia. Hartman, F. A. and G. W. Thorn, Proc. Soc. Exper. Biol. & Med. **29**: 48. 1931.

Four normal persons showed considerably greater resistance to muscular fatigue as measured by ergometer tests, after injections of cortin. Of two patients with Addison's disease in which the cortical insufficiency was almost absolute, one showed 700% increase in the ability to do work without fatigue and the other showed no effect after cortin treatment. In two less severe cases, there were 400 and 4900% increases and in two other cases no effect. A patient with asthenia during pregnancy was markedly benefited by treatment. In a case of Graves' disease, one of muscular dystrophy, two of osteomyelitis in children and one of persistent asthenia following diphtheria marked improvements were noted. In a case of marked neurasthenia and in one of myasthenia gravis no improvement was secured.—M. O. L.

Accessory adrenals in rat (El problema de las suprarrenales accesorias de la rata). Lascano-Gonzalez, J. M., Doctorate Thesis. Med. Univ., Nat. Buenos Aires, 1932.

Bilateral adrenalectomy was performed in a large number of white and piebald rats and they were observed for different periods of time up to one year. Growth was not modified when young rats were operated upon. Mortality was low; 55% were living 8 months after and 30% one year after the operation. These figures nevertheless do not show the true effect of adrenalectomy, as such, because epidemic broncho-pneumonia occurred and increased the mortality. All animals (51) observed between the 8th and 12th month following operation had macroscopically visible accessory adrenal tissue in the region between the kidneys and the diaphragm. In 81% of animals killed 45 days after adrenalectomy and only in 35% of those killed 15 days after the operation accessory adrenals were found, although all the tissue

situated retroperitoneally between the kidneys and diaphram were cut serially and observed microscopically. Of all the accessory bodies studied only 2 (4%) had cortical and medullary tissue; the others were made up exclusively of cortical cells. These were distributed irregularly and belonged principally to the fasciculate type (spongiocytes). In 4 normal rats serial sections of the retroperitoneal tissue were made and in all of them accessory adrenals were found. The small number of observations does not permit one to say that all rats have these bodies, especially as they were not found in a certain number of recently adrenalectomized rats. After operation these microscopic bodies become hypertrophied and may become visible to the naked eye. Their gradual development may be responsible for the functional compensation that gradually takes place in this species. The fact that they are almost always made up of cortical cells only is a further proof of the importance to life of this tissue. Nevertheless they may not be the only factor concerned since in a few cases survival of 15 days and even 45 days occurred when no accessories could be found. It would be better to consider the hypertrophy of the accessories as a consequence of survival, facilitating it, but not its principal cause. The lymph glands were considerably hypertrophied and the thymus remained visible and enlarged at ages when usually it is found with difficulty on a macroscopical observation only. The sex glands were not affected.

—J. T. Lewis.

Glycogenolytic effect of epinephrine on skeletal muscle. Major, S. G. and F. C. Mann, Am. J. Physiol. **101**: 462. 1932.

Changes of dosage of iso-amylethyl barbiturate was found to cause little, if any, alteration in the glycogen content of skeletal muscle in dogs. Massive doses of epinephrine (5 experiments) caused a marked decrease of glycogen in the muscles as shown by the comparison of pairs (or parts) one extirpated before and one after the injection. Doses of the substance as small as 0.00016 mgm. for each kgm. for each minute caused definite glycogenolysis in 3 experiments, whereas 0.000066 mgm. for each kgm. of body weight each minute did not result in demonstrable alteration in glycogen. The former dose was not attended by elevation of the arterial blood pressure or diminution of limb volume.—R. G. H.

Effect of adrenal cortex extract on the course of certain human infections. Whitehead, R. W. and C. Smith, Proc. Soc. Exper. Biol. & Med. **29**: 672. 1932.

Five patients with various infections and marked fever were treated with adrenal cortex extract with beneficial results. One case was a typical typhoid fever, one was undulant fever of 6 weeks' duration, one was post-operative erysipelas, one was lymphangitis of the hand and arm with Micrococcus aureus present in the blood, and the fifth case was diagnosed as virulent ethmoid sinus infection and peribronchial adenitis. The dosages of extract given represented 100 to 200 grams of fresh gland. Marked improvement and normalizing of the temperature was noted in every case, although the patient with erysipelas later suffered a relapse and died before a second injection could be given.—M. O. L.

Metabolic and hormonal influences affecting tumor grafts (Influences métaboliques et hormonales sur le développement des greffes cancéreuses). Craciun, E. C., Compt. rend. Soc. de biol. **111**: 137. 1929.

Pieces of fixed size from various kinds of normal tissues were implanted into white rats and with each piece was placed a graft of Jensen sarcoma. After three weeks the tumor was measured. From 9 to 15 rats were used to test each combination. The tumors implanted with liver and spleen were inhibited in their growth. Those combined with thyroid or testicle were stimulated to more active growth than control tumors.—J. C. D.

The respiratory quotient of the brain. Himwich, H. E. and L. H. Nahum, Am. J. Physiol. **101**: 446. 1932.

The respiratory quotient of the brain of 14 dogs (1 unanesthetized, 4 amytalized, 4 phlorhizinized, 4 depancreatized and 1 depancreatized and phlorhizinized) has been determined by analysis of the arterial and venous blood for

carbon dioxide and oxygen by the method of Van Slyke and Neill. The average of the 38 respiratory quotients thus obtained was 1.00 ±0.006 and the average deviation of a single result was ±0.035. Four unanesthetized animals were studied after injection of pituitrin or pitressin and 7 dogs under amytal anesthesia were examined after injections of insulin or adrenaline. The respiratory quotient was not changed by insulin or pituitrin, although it was by adrenaline and pitressin, probably because of shifts in the water, electrolyte and acid-base equilibria. Carbohydrate is constantly oxidized by the brain of the living animal. Since the respiratory quotient remains uniform after pancreatectomy carbohydrate is not utilized in the form of glucose. It has been calculated that the oxygen consumption of dog brain is 14 cc. per 100 grams of tissue per minute.—Authors' Summary.

Factors influencing experimentally produced convulsions. Keith, H. M., Arch. Neurol. & Psychiat. **29:** 148. 1933.

In experiments on rabbits it was found that epinephrine, pituitrin S and pitressin greatly augment the convulsant action of the poison thujone, and the action of epinephrine, and pitressin persists for at least three minutes after intravenous injection. These drugs will cause a subconvulsant dose to become convulsant. Epinephrine eliminates the refractory period due to the administration of thujone. The administration of desiccated thyroid gland and thyroxine did not definitely increase the susceptibility of the rabbits to thujone. The administration of insulin to rabbits with resulting hypoglycemia did not increase their susceptibility to convulsions.—R. G. H.

Ketosis in the pancreatic and phlorrhizin diabetes of hypophysectomized dogs. Rieth, C. T., J. Physiol. **77:** 92. 1932.

Ketone elimination was only one-third to one-fourth as great in hypophysectomized dogs as in controls, and phlorrhizin was only one-seventeenth. After thyroidectomy, posterior lobe pituitary extirpation or lesions of the tuber cinereum ketone elimination was greater than in controls.—C. I. R.

Thyroxine-prolan therapy for obesity of women with early amenorrhea (Thyroxine-Prolan Behandlung der Fettsucht frühzeitig amenorrhoischer Frauen). Schittenhelm, A. and B. Eisler, Klin. Wchnschr. **11:** 446. 1932.

In two cases the authors had good results. They gave thyroxine (Schering) per os 6-9 mgm. per day for three or four days, then 80-300 M. units of Prolan A and B.—E. Kodicek.

Basal metabolism of twenty-one Chinese children reared or born in the United States. Wang, C. C. and J. E. Hawks, Am. J. Dis. Child. **44:** 68. 1932.

The basal metabolic rate of 21 Chinese-American children, 11 boys and 10 girls between 5 and 17 years of age, was studied. The results of this investigation were closely comparable to the findings in the group of American children classified as "normal in weight but not vigorous," who were studied by the authors in connection with the problem on undernourished children. The present study has failed to demonstrate a definite low basal metabolism in Chinese-American children such as several investigators found in Oriental adults. Some of the possible causes of the discrepancy between the present findings and those reported in the literature are: (1) the difference in climatic conditions; (2) the difference in standards in adults and in children, and (3) the difference in the ability to relax in adults, especially Oriental adults, and children.—M. B. G.

Studies on the physiology of reproduction; effect of thymectomy and of season on the age and weight at puberty in the female rat. Andersen, Dorothy H., J. Physiol. **74:** 49. 1932.

A statistical analysis of results of three series of female rats, totalling 89 operated and 85 controls. Judging the onset of puberty by the opening of the vagina, thymectomy, regardless of the age at the time of operation, did not alter the age or weight at puberty, the age of oestrus, the growth, appearance or behavior, the actual or relative weights of other organs.—C. I. R.

Studies on the physiology of reproduction; effect of thymectomy on the age of puberty in the male rat. Andersen, Dorothy H., J. Physiol. **74**: 207. 1932. **III. The effect of thymectomy on fertility in the rat.** Ibid., P. 212.

The age of puberty in male rats was determined by killing groups at intervals and examining for mobile sperm. A series of 40 rats were thymectomized at 21-22 days. The operation did not affect the age of puberty nor any other factor listed in the preceding paper. A series of 54 rats used in the experiments reported in the first paper were saved for mating experiments. The operation did not affect fertility. The author concludes that the results of these investigations constitute evidence against a direct relation between thymus and gonads.—C. I. R.

Fifty cases of the Aschheim-Zondek test applied to male and female rats (A propos de 50 cas de reaction d'Aschheim-Zondek appliquee au rat male et femelle). Bourg, R., Le Scalpel, **84**: 1421. 1931. Abst., Rev. belge sc. med. **3**: 1096.

To escape the 5% error of the Aschheim-Zondek reaction and the possible errors of the method of injecting urine of pregnant women into male rats the author considers that the two reactions used simultaneously ought to be in agreement in affirming whether or not the urine is from a pregnant woman.
—Translated by J. Gagnon.

Placental hormones. Collip, J. B., Internat. Clin. **4**: 51. 1932.

Extract of fresh human placenta, or of human placenta frozen while fresh, may be separated into the following hormone fractions: (1) An ether-insoluble oestrogenic fraction, (2) an ether-soluble oestrogenic fraction, and (3) an anterior-pituitary-like hormone fraction. Young female rats 21 days old treated with fraction one showed an oestrogenic effect on the third to fifth day following the oral administration of adequate dosage, but even long-continued administration neither accelerated nor diminished the rate of development of the ovaries. The administration of emmenin produces regular oestrus cycles in acyclic but otherwise normal adult female rats. Normal adults show no deviation when thus treated and pregnancy in pregnant rats is not interfered with. Fraction one shows greater activity when administered orally than by subcutaneous injection. The point of greatest importance to the mind of the writer is the fact that there exists in placenta and in pregnancy blood and urine an organic complex which is freely water-soluble and which contains in chemical combination an active oestrogenic substance which, while in such combination, is highly active in the production of oestrus in intact immature female animals, but which manifests only slight activity when administered to adult castrated animals. Fraction two, keto-hydroxy-oestrin or theelin is more effective on the adult castrated animal than on the immature normal. It shows no difference in its action on ovariectomized immature animals implanted in the spleen with two normal immature ovaries and in similar ovariectomized animals without such implants. Immature normal hypophysectomized animals show sensitivity to theelin. These facts are in direct contrast to the action of the tri-hydroxy-oestrin similarly prepared by Doisy. Adult ovariectomized animals that have become immune to the oestrogenic action of the tri-hydroxy-oestrin have been found to be still sensitive to the keto-hydroxy form and after the production of vaginal oestrus by the latter have responded again to the tri-hydroxy form. With respect to fraction three the author finds that the parallelism between the physiological activity of this partially purified hormone fraction of the human placenta and the sex hormone of the anterior pituitary lobe breaks down under comparative long-term experiments. The question now being worked on is whether the placental principle will replace the pituitary sex hormone in completely hypophysectomized animals. The author feels that normal morphogenetic and trophic action of the pituitary cannot be substituted by anterior pituitary lobe injection. The atrophy of male and female gonads following hypophysectomy could never be prevented by anterior pituitary lobe treatment. This substance administered to pre-pubertal female rats for long periods caused a succession of fairly regular oestrus cycles, a post-pubertal state having been induced. On the other hand, the daily implantation of fresh rat pituitary and the daily injection of untreated fresh pregnancy urine led to identical results, namely, early suppression of oestrus cycles and the development of enormous and extensively luteinized ovaries. They returned to normal

in a few weeks. Anterior pituitary lobe has a profound effect on the male rat, which is manifested in the degree of development of the accessory organs of either the immature or the adult male animal treated with the active extract. These return to normal after a few months of treatment. None of the anterior pituitary lobe activity has been found in the urine or tissues of the lower animals with the possible exception of the mare. The placenta of the dog, rabbit, rat, pig, cow, or monkey show no such activity. Emmenin has been most satisfactory clinically in dysmenorrhea when no pathological condition was present in the pelvis. No alteration was noted in the normal cycles of 10 control cases. Certain types of secondary amenorrhea of recent origin responded favorably. Menopausal symptoms of recent origin were relieved in many cases, but castrates were not benefited.—I. B.

The relation of emmenin to other oestrogenic hormones. Collip, J. B., J. S. L. Browne and D. L. Thomson, Proceedings of the Fourteenth International Congress of Physiology, P. 56. 1932.

Administration of the placental hormone, emmenin, to normal immature female rats results in the production of the phenomena of oestrus. The dose required for the production of oestrus in the adult ovariectomized animal is several times that required to produce oestrus in the intact immature female. Crystalline products have been obtained both from extracts of human placenta and of the urine of pregnancy which have these above mentioned physiological properties. The relationship of this substance to other oestrogenic hormones has been extensively studied. Evidence is submitted to show that the active principle emmenin is present in the crude extract in two forms: one fraction may be extracted from an aqueous solution with ether, the other cannot be extracted with ether but part of it at least becomes ether-extractable following hydrolysis in the high pressure autoclave at a temperature of 180 degrees for three hours in the presence of 1% acetic acid. Hydrolysis in a water bath in the presence of 5% sulphuric acid does not, however, increase to any appreciable extent the ether extractability of this active principle and treatment, if prolonged, results in a considerable reduction in the potency of the extract. —M. O. L.

Histological modifications of the hypophysis of the guinea pig during pseudo-gestation (Les modifications histologiques de l'hypophyse au cours de la psuedogestation chez le cobaye). Desclin, L. and L. Brouha, Soc. belge de Biologie, **107**: 895. 1931. Abst., Rev. belge sc. med. **3**: 1098.

During pseudo-gestation the anterior lobe of the hypophysis presents the same modifications as during normal pregnancy when the pseudo-gestation is prolonged to the extent of a normal gestation; the hypophyseal reactions are the same qualitatively and quantitatively. Thus, in the absence of the foetus, foetal placenta and maternal placenta in the uterus, the pregnancy changes in the hypophysis can take place. These changes, therefore, are not due to the specific action of these elements but are due to the changes taking place in the ovary which are the same in gestation and pseudo-gestation.
—Translated by J. Gagnon.

Method for prediction of sex in the unborn. Dorn, J. H. and E. I. Sugarman, J. A. M. A. **99**: 1659. 1932. Abst., A. M. A.

By injecting rabbits, fully 3 months old, whose testes were in the inguinal canal, with urine from women in between five and ten months of pregnancy, the authors were able to prognosticate the sex of the unborn child in 80 of 85 cases. The basis for their prognosis was the microscopic changes in the testis of the rabbit, noted forty-eight hours after injection. The testes of the rabbits injected with urine from women carrying an unborn female child were developed precociously. The testes of the rabbits injected with urine from women carrying an unborn male child were not so stimulated.

Ovarian implantation. Estes, W. L., Jr., Internat. Clin. **3**: 367. 1932.

No operation devised for sterility yields a high percentage of subsequent pregnancy when bilateral tubal disease exists. Salpingostomy or implantation of a tube may be considered when a portion of at least one tube seems normal. Ovarian implantation preserves menstruation and seems to offer a remote possibility for pregnancy when both tubes must be completely sacrificed.—I. B.

The influence of the female sex hormone on the young male sex glands (Über den Einfluss der weiblichen Geschlechtshormone auf die juvenilen männlichen Keimdrüsen). Gereb, P., Ztschr. f. Geburtsh. u. Gynäk. **99**: 443. 1931.

The author observes, in about 85% of the cases, an increase of spermatogenesis and hypertrophy of the generative glands following an injection of 0.3-0.4 cc. of filtered urine from pregnant women into young (16-20-day) male, white, mice weighing 3.5-4.5 gm. 2-3 times a day for 4 days. When the urine has been brought to 100° C. for 1-2 minutes, a treatment which destroys the anterior pituitary hormone (Prolan) but not the female sex hormone, and the above procedure is repeated, about 70% of the mice show a microscopic picture identical with the first group. In 20 cases there was no change noted when heated urine, extracted with ether (this removes the female sex hormone), was injected.—R. A. Phillips.

Studies on sex physiology. Ovulation brought about by the luteinizing hormone Prolan B (Geschlechtsphysiologische Studien; Ovulation ausgelöst durch das Luteinisierungshormon Prolan B). Gostimirovic, D., München med. Wchnschr. **78**: 1350. 1931.

The urine of a 45-year-old patient with cancer of the cervix was prepared by the method of Zondek and concentrated to one-tenth the original volume. A litter of six immature female mice weighing from 3.6 gm. to 6.3 gm. and 25 days of age were employed as test animals. One animal was retained as a control and 5 were given 1.2 ccm. of the urinary preparation in 6 injections in 48 hours. Three of the experimental animals and the control died before the completion of the experiment. The remaining two animals became sick about 70 hours after the first injection, and their genital tracts were fixed immediately after their death a short while later. Histological examination of the ovaries and tubes show that ovulation had occurred in both animals. This ovulation was not accompanied by any sign of a Prolan A effect, but considerable luteinization was associated with it. It is consequently apparent that the luteinizing hormone, Prolan B, is responsible for ovulation.—F. L. Hisaw.

The amount of folliculin in the blood of pregnant women and its distribution between the cells and the plasma (De la teneur en folliculine du sang des Femmes enceintes, et de la répartition de la folliculine entre les globules et le plasma). Kemp, T. and K. P. Bjergaard, Compt. rend. Soc. de biol. **111**: 329. 1932.

The urine was found to contain 12 to 18 times more folliculin per liter than the blood. This folliculin was divided about equally between cells and plasma. The material came from six healthy women in the 9th month of pregnancy.—J. C. D.

Cyclic variations in pulse rate in women and their relationship to the menstrual cycle. Moore, Lillian M. and Lulu Marie Jenkins, Proc. Soc. Exper. Biol. & Med. **28**: 997. 1931.

The daily pulse rates of 7 women observed over periods of 2 to 13 months vary with each phase of the menstrual cycle and in no case show a static norm. The pulse rate progressively increases during the phase of the cycle representative of the greatest activity (glandular and otherwise) of the genital tract; i.e., from the end of the 1st to the end of the 3rd week of the menstrual cycle. It progressively decreased during the following two weeks of lessened activity, the lowest point being reached near the end of or after the completion of menstruation. The rhythm in pulse rate shows a significant resemblance to the rhythm in the primary events of the menstrual cycle.—Authors' Summary.

An investigation of the "pregnancy reactions" 'in the infantile sex organs (Histologische und experimentelle Untersuchungen zur Frage der Schwangerschaftsreaktion der Neugeborenengonaden). Neumann, H. O., Ztschr. f. Geburtsh. u. Gynäk. **99**: 100. 1931.

The author has studied the effect of ovarian and hypophyseal hormones in the urine and blood serum of the umbilical cord from new-born infants. Using, in white mice, the testicular size, the size of the accessory sex organs in the male both normal and castrated, the microscopic picture of the ovaries, and the uterine size and the size of the mammae in castrated male guinea pigs

he concludes that ovarian hormone and anterior pituitary hormone are present in the new-born human but that after 3 days the amounts of these hormones decrease, the former decreasing more rapidly than the latter. He concludes that the effect of the anterior pituitary hormone in causing hypertrophy of the accessory sex organs in the male is accomplished through the testes. He also found in the urine of 32 out of 43 examinations of individuals up to the age of 10 a substance which would cause hypertrophy of the uterus and ovaries in female white mice. This is postulated as an effect of the "growth-stimulating hormone." There is an extensive bibliography, and complete description of the technique. The photographs are good.—R. A. Phillips.

Pregnancy changes in the rabbit's uterus and their relation to endocrine activity. III. Robson, J. M., Quart. J. Exper. Physiol. **22**: 209. 1932.

A further investigation of the relation of the anterior pituitary hormones to ovarian and uterine changes in mature female rabbits by daily injection of anterior lobe tissue. The animals were previously examined for pregnancy or pseudopregnancy. Examination by laparotomy on the seventh day revealed luteinization. Uterine biopsy established the condition of the endometrium, usually marked progestational proliferation. The muscle responded strongly to pituitrin in contrast to the response of the normal uterus or after a single injection of anterior lobe. This the author terms dissociation of uterine responses. Simultaneous injection of standard corpus luteum extract did not usually cause inhibition of the pituitrin response. Gonadotropic preparations from pregnancy urine failed to give this result. Simultaneous injections of anterior lobe extract and a-hormone (oestrin) indicated that the latter is essential for the development of the inhibitory reaction.—C. I. R.

Standardization of male sex hormone (Zur Standardisierung des Männlichen Sexualhormons). Schoeller, W. and M. Gehrke, Wien. Arch. f. inn. Med. **21**: 329. 1931.

The authors develop a capon unit upon the reaction of the White Leghorn capon comb to injection of male hormone. This unit they define as the quantity of male hormone which injected twice, at 24-hour intervals, yields an average comb growth in three animals of 20% when measured at the end of 48 hours. To calculate the comb growth they photograph the comb and then measure the outline with a planimeter. To get the percentage they use Laqueur's formula (b-a) 100—a, where b equals the comb area at the end, and a equals the comb area at the beginning of the experiment. The authors were apparently unfamiliar with the earlier defined bird unit of Gallagher and Koch.—I. B. Hansen.

Manganese as a factor in reproduction. Skinner, J. T., Evelyn Van Donk and H. Steenbock, Am. J. Physiol. **101**: 591. 1932

Female rats reared on whole milk fortified with copper and iron did not attain sexual maturity, as indicated by establishment of the vaginal orifice, as early as those receiving the same ration supplemented with manganese. Females receiving a manganese supplement did not exhibit normal oestrous cycles. Like those on the milk-iron-copper diet, they often failed to exhibit oestrum over long periods of time and when cycles occurred, they were less frequent than in the normal animal. Females receiving sucrose and manganese in addition to the basal ration exhibited normal oestrous cycles of 4.3 days' duration. Those given sucrose but no manganese performed less satisfactorily. When a food mixture (liver, yeast, egg yolk, cod liver oil and wheat germ oil) was added to the basal diet, oestrous cycles occurred at intervals slightly longer than normal, namely, 5 days.—Authors' Summary.

The inhibition of lactation in rabbits with large amounts of oestrin. Smith, G. V. S. and O. W. Smith, Am. J. Physiol. **103**: 356. 1933.

Three rabbits with retained living placental remnants failed to lactate. The ovaries of each contained large corpora lutea. The administration of large amounts of oestrin to several rabbits after delivery, to those exhibiting spontaneous lactation or to those lactating following pseudopregnancy, resulted in

a marked decrease or total disappearance of the secretion. In two cases simultaneous administration of pituitary extract and theelin failed to cause lactation. The possibility of an interrelationship between oestrin and the lactation factor of the pituitary is discussed.—R. G. H.

The ovary of the rat after hypophysectomy. Swezy, O. and R. I. Pencharz, California & West. Med. **38**: 97. 1933.

Eight rats were autopsied at dates varying from 12 to 90 days after hypophysectomy. Counts of all ova and follicles contained in one ovary of each animal were compared with similar counts made on normal controls. It was found that the number of ova and follicles in the hypophysectomized rats was about twice the total number of ova and follicles in the controls. There were abundant evidences of the new formation of germ cells from the germinal epithelium and of mitoses in the granulosa of small follicles, as well as much atresia among both ova and follicles, indicating that the larger numbers were not due to an accumulation but to an actual increase in the production of germ cells. This increase in the rate of ovogenesis seems to be due solely to the withdrawal of the hormones of the anterior pituitary.—Olive Swezy.

Ovarian follicle hormone therapy in ovarian insufficiency and the menopause. Webster, B., Am. J. M. Sc. **184**: 822. 1932.

A series of 20 cases is presented in which the intravaginal administration of the ovarian follicle hormone has been alternated with control periods. It would appear that the preparation of the hormone used was physiologically active in women as evidenced by the induction of uterine bleeding. Further, data are presented which suggest that this hormone of the ovarian follicle is of definite clinical therapeutic value in the treatment of the disagreeable symptoms which may accompany the menopause and of the amenorrhea due to an insufficiency of that hormone. No beneficial results were obtained when the hormone was administered in cases of amenorrhea with accompanying clinical evidences of an anterior pituitary etiology.

The treatment of retinitis pigmentosa with female sex hormone (Menformon) (Behandlung von Retinitis pigmentosa mit weiblichen Hormon [Menformon]). Wibaut, F., Deutsche med. Wchnschr. **57**: 1739. 1931.

Retinitis pigmentosa occurs more frequently in men than in women and is more serious in men. Because of this predisposition the author regards it rather as a secondary sex characteristic than as a characteristic bound in with the sex chromosome. This fact gave rise to the theory that the cause for the diminished frequency and severity in the female resides in a hormone which exists in the female organisms and influences favorably the course of the disease. On the basis of this theory Menformon was employed with which good results were obtained. Spontaneous improvement is not known to occur in this disease. The therapeutic effect of Menformon was determined by its effect in the visual fields and consciousness to light. Of the five patients treated, one was greatly benefited, two noticeably improved, one slightly improved, and one of long standing remained unimproved.—H. S. Beck.

Phlorrhizin diabetes in fasting or fed hypophysectomized dogs. Biasotti, A. and B. A. Houssay, J. Physiol. **77**: 81. 1932.

A study of 31 fasting dogs, 7 hypophysectomized, 4 with posterior lobe removed, 9 with lesions of the tuber cinereum, 6 thyroidectomized and 5 controls. Compared to the controls, fasting hypophysectomized dogs did not exhibit as severe a degree of phlorrhizin glucosuria, which is believed to be due to absence of the anterior lobe, since it did not occur after removal of the posterior lobe or thyroid nor after lesions of the tuber. The fatal hyperglycemia was prevented by diets of meat or sugar but not by fat. This suggests that the fundamental effect of hypophysectomy is a limitation of capacity to form glucose from tissue protein. Fasting nitrogen elimination was decreased after hypophysectomy or thyroidectomy as compared to controls or those with tuber lesions. After phlorrhizin, fasting elimination of nitrogen was also lower in those two groups.—C. I. R.

Sexual function of the hypophysis; contribution to the study of hormonal determination of sexual phenomena (La fonction sexuelle de l'hypophyse. Contribution à l'étude du déterminisme humoral des phénomènes sexuels). Brouha, L., Arch. internat. de physiol. **33:** 1. 1930. Abst., Rev. belge sc. med. **3:** 1097.

The problems studied in this work apply only to mammals. The author confirms facts furnished by others and adds numerous new observations. In the normal individual the sex life depends directly upon the presence of the sex glands, ovaries or testicles, even if the reproductive cells are destroyed. This action is controlled by hormones. The injection of these hormones into castrated animals compensates fully in the female and partially in the male for the ablation of the sexual organs. The ablation of the anterior lobe of the hypophysis causes a functional castration, in the presence of the sex glands. The implantation of the anterior lobe of the hypophysis causes this trouble to disappear, thus indicating that the action is hormonal. The implantation of the hypophysis, whatever the sex of the receiver, and regardless of the sex and genital condition of the donor, causes a stimulation of the sexual processes. This action takes place only if the receiving animal has its sex glands. Consequently it may be said that there is a functional correlation between the anterior lobe of the hypophysis and the endocrine activity of the sex glands. Extracts prepared from the anterior lobe of the hypophysis in an acid or neutral medium have the same action as transplants of fresh glands in stimulating the sex glands of male and female animals while extracts prepared in alkaline solutions only affect females. The blood, urine, and placenta of pregnant women as well as their extracts prepared in an acid or neutral medium act on the male and female sex glands; alkaline extracts act only on the female sex glands. One finds similar properties in some extracts of corpora lutea and of the epiphyses prepared in acid or alkaline media. This brings up the question whether the anterior lobe of the hypophysis acts through only one hormone or through two sexually differentiated hormones.—Translated by J. Gagnon.

Hypophysis and thyroid. Thyroids of young guinea pigs as indicators for testing the thyroid-stimulating properties of serum (Hypophyse et thyroïde des jeunes Cobayes comme réactif pour déceler l'activité thyréo-stimulatrice du sérum). del Castillo, E. B., Compt. rend. Soc. de biol. **111:** 461. 1932.

The thyroids of 12 of 15 normal guinea pigs between 150 and 230 grams body weight showed histological evidence of activity. Stimulation of a quiescent thyroid has been used as a test for the presence of hypophyseal secretion. It appears that the thyroids of young guinea pigs are not suitable indicators for this test.—J. C. D.

Connections of the hypophysis in the guinea pig with the meninges, the sella turcica and the marrow spaces of the sphenoid bone (Connexions de la glande pituitaire avec les méninges de la selle turcique et les espaces médullaires du sphénoïde chez le Cobaye). Collin, R., Compt. rend. Soc. de biol. **111:** 67. 1932.

The perihypophyseal venous sinus is described. This extends between the gland capsule and the periosteum. It connects with the cavernous and coronary sinus peripherally and with the marrow spaces of the sphenoid below. Into it, drain veins from both lobes of the gland.—J. C. D.

The basophil adenomas of the pituitary body and their clinical manifestations (pituitary basophilism). Cushing, H., Bull. Johns Hopkins Hosp. **50:** 137. 1932. Abst. Canad. M. A. J. **27:** 214.

Twelve cases of a polyglandular syndrome hitherto supposed to be of cortico-adrenal origin are discussed. Six out of 8 of these have been found at autopsy to be associated with a pituitary adenoma which in the 3 most carefully studied cases has been definitely shown to be composed of basophilic elements. All of these cases showed the following characteristic features: (1) a rapidly acquired, peculiarly disposed and usually painful adiposity; (2) a tendency to become round-shouldered, associated with lumbo-spinal pains; (3) a sexual dystrophy shown by early amenorrhoea in the females and ultimate functional impotence in the males; (4) a tendency to hypertrichosis of face and trunk in all the females as well as preadolescent males, and possibly the

reverse in the adult males; (5) a dusky or plethoric appearance of the skin, with purplish lineae atrophicae; (6) variable backaches, abdominal pains, fatigability and ultimate extreme weakness. The average duration of life of the fatal cases was five years, and all the patients succumbed to progressive enfeeblement associated in most cases with terminal infections. One of the two patients reported from the author's clinic who appeared to be rapidly approaching his end was given four x-ray treatments and made a remarkable recovery. While the evidence in favor of the relation of this syndrome only to basophilic adenomas of the pituitary body is still somewhat equivocal, this article will provide pathologists with greater stimulus to carefully search the anterior pituitary for such lesions.

Effect of artificial luteinization in the ovary on the structure of the anterior lobe of the hypophysis in guinea pigs (Influence de la lutéinisation provoquée de l'ovaire sur la structure du lobe antérieur de l'hypophyse chez le Cobaye). Desclin, L., Compt. rend. Soc. de biol. **111**: 1085. 1932.

The formation of corpora lutea was induced by injections of urine from pregnant women. The hypophyses of the guinea pigs showed histologically the same changes as seen in pregnancy. The corpora lutea, therefore, not the placenta or fetus, are the source of the effect on the hypophysis.—J. C. D.

The presence in the blood of pregnant women of a substance antagonistic to the oxytocic action of the posterior pituitary (Sur la présence dans le sang de la femme enceinte d'une "substance empachante" de l'action ocytocique du lobe postérieur d'hypophyse. Sa disparition à l'accouchement). Dodel, P., Proceedings of the Fourteenth International Congress of Physiology, P. 68. 1932.

Blood serum of pregnant women inhibits the stimulating action of posterior pituitary extract on the isolated oviduct of Vipera aspis. Serum from non-pregnant women has no such antagonistic effect, nor does serum from women in labor or a few days post-partum. The author concludes that there exists in the serum during pregnancy a hormone opposing the oxytocic effects of the pituitary and that labor is caused by the disappearance of this hormone. He suggests that the origin of the substance is from the placenta.—M. O. L.

The roentgenotherapy of pituitary tumors. Dyke, C. G. and S. W. Gross, Bull. Neurol. Inst. **1**: 159. 1931. Abst. Arch. Neurol. & Psychiat. **29**: 1933.

The authors present studies of the case histories of five patients in which a diagnosis of pituitary tumor had been made, and in which the patients were treated by roentgenotherapy. In all the patients headache was entirely relieved following roentgenotherapy; three patients showed marked improvement in visual fields and visual acuity; two patients lost considerable weight; two patients showed no improvement of vision, but there was no further loss of vision, and subjectively they seemed somewhat improved. The authors express the opinion that roentgenotherapy must be prolonged and vigorous and that treatment must be continued even though favorable results are obtained after the first series of treatments. The importance of charting visual fields and acuity after every roentgen treatment is emphasized as the best guide to the patient's reaction.

The effect of posterior pituitary extracts on the glycogen content of liver and muscles (Über die Wirkung der Hypophysenhinterlappenauszüge auf den Glykogengehalt der Leber und der Muskeln). Gömöri, P. and P. Marsovszky, Arch. f. exper. Path. u. Pharmakol. **165**: 516. 1932.

The authors report that in white rats there was a 57% decrease of liver glycogen and no change of the glycogen content of muscle 3 hours after the injection subcutaneously and intravenously of 1 ccm. of Pituitrin. The results of 24 injected animals are averaged against the results of 24 control rats to obtain the quoted figures.—R. A. Phillips.

Radiotherapy of pituitary tumors. Harris, W. and H. Selinsky, Radiology, **18**: 777. 1932. Abst. Am. J. M. Sc. **184**: 1932.

Thirteen cases of pituitary tumor were subjected to roentgen ray therapy and observed at tri-monthly intervals. Seven of the 13 patients were distinctly

benefited by the treatment and one showed temporary improvement. Amelioration of headache and improvement in vision were most frequently noted. In no case did the symptoms completely disappear. Failure to respond to treatment is highly suggestive of a cystic tumor (craniopharyngeal pouch cyst).

The significance of pituitrin in the physiology of pregnancy (Über die Bedeutung des Pituitrins in der Physiologie der Geburt). Heller, J. and P. Holtz, Klin. Wchnschr. **10:** 1767. 1931.

Anterior pituitary hormone (Prolan) and an increased K content of the surrounding fluid sensitize the isolated rabbit's uterus to the action of pituitrin. Ovarian hormone which has been freed of the protein fraction (estrogen and progynon) does not have this action. The authors conclude that at the end of pregnancy an increased production of pituitrin acts upon the uterus, which has already been sensitized by an increased production of Prolan and an increase of the K:Ca ratio of the blood, to initiate labor.—R. A. Phillips.

Macrogenitosomia praecox associated with an ependymoglioma of the mammary region. Heuyer, G., J. Lhermitte, de Martel and C. Vogt, Rev. neurol. **2:** 194. 1931. Abst. Arch. Neurol. & Psychiat. **28:** 1932.

A boy, aged 6 years, developed with abnormal rapidity and presented the physical appearance of a lad of 12. The sexual organs were especially well developed, with a good growth of hair. The patient suffered from headache, which was worse on quick movements of the head; he walked a little gingerly, but he had never had any vomiting or convulsive seizures. The reflexes were active, with plantar extension on the left. There was no somnolence, glycosuria or polyuria. The cranial nerves were normal. Mentally, he appeared backward, and a mental age of 3 years had been reported. The sella turcica was small; the convolutional markings were visible in the roentgenogram. The spinal fluid escaped under increased pressure but showed no abnormal elements. The epiphyseal region was explored without anything abnormal being found, and the child died two days after exploration. Serial sections through the region of the tuber cinereum showed a cystic tumor, apparently originating in the right mammillary body, causing slight compression of the surrounding structures, with dilatation of the aqueduct of Sylvius, but no evident pressure on the optic nerve. The epiphysis was entirely normal.

Effect of posterior pituitary extracts on the constituents of the blood. Himwich, H. E., F. W. Haynes and J. F. Fazikas, Am. J. Physiol. **101:** 711. 1932.

Observations of the effects of pitressin, pitocin and pituitrin on plasma glucose, lactic acid and total solids were made on 17 amytalized, 21 unanesthetized and 2 decerebrate dogs. Pitressin, pitocin and pituitrin increased the blood glucose in unanesthetized animals but often lowered it in amytalized animals. Pitressin increased plasma lactic acid in unanesthetized dogs whereas pitocin had little effect. Pitressin and pitocin probably cause a dilution of the blood similar to that observed after pituitrin.—Authors' Summary.

Pituitary and thyroid; compensatory hypertrophy of the thyroid (Hipofisis y tiroides; Hipófisis e hipertrofia compensadora de la tiroides). Houssay, B. A., A. Biasotti and A. Magdalena, Rev. Soc. argent. de biol. **8:** 13. 1932.

Total hypophysectomy was practiced in 9 dogs and later a subtotal thyroidectomy, leaving not more than 0.05 gm. of thyroid tissue (with the parathyroids) on each side. One and two months later these remnants were removed and examined microscopically. No compensatory hypertrophy was seen; the vesicular epithelium had the same aspect as when the thyroid was extirpated except in one case in which a definite hypertrophy was observed; the height of the vesicular epithelium rose from 3.88 to 12.6 micro (average of measurings taken in 30 vesicles). Serial sections of the pituitary region revealed a remnant of anterior pituitary lobe measuring 2.5x1x1.5 mm. in this case; in the others no anterior lobe tissue was found except in one a minute piece (0.1x0.1 mm.). Pars intermedia tissue was found adhering to the infundibulum. Subtotal thyroidectomy was also performed in normal dogs, in dogs that had suffered a simple craniotomy (4) and in 5 dogs with lesions produced by cauterization of the tuber cinereum, one dog of which had the posterior pituitary lobe destroyed. In all these, compensatory hypertrophy of the remaining thyroid tissue was observed, as shown by the microscopical

aspect and the increase in height of the vesicular epithelium that was measured. Three hypophysectomized dogs received intraperitoneal injections of alkaline extract of anterior pituitary lobe (Evans and Simpson's, 1931, growth factor). After subtotal thyroidectomy all showed definite compensatory hypertrophy and in numerous places zones of hyperactivity were seen in the remaining thyroid tissue. The authors conclude that a secretion of the anterior pituitary lobe is a necessary factor in the production of compensatory hypertrophy of the thyroid.—J. T. Lewis.

Diabetogenic activity of anterior pituitary lobe extract (Acción diabetógena del extracto antero-hipofisario). Houssay, B. A., A. Biasotti and C. T. Rietti, Rev. Soc. argent. de biol. **8**: 469. 1932.

Intraperitoneal injection of Evans and Simpson's anterior pituitary lobe extract (10 cc.=2 gm. fresh gland daily) produced in rats polyuria, glycosuria (11.5—40 gm. %) and raised the blood sugar from 0.083—0.135 gm. % found in controls to 0.140—0.170 gm. %. Normal dogs receiving 7 cc. per kgm. daily had glycosuria up to 1 and 1.7 gm. per kgm. per day; fasting blood sugars varied between 0.170 and 0.270 gm. %; ketone bodies in the urine rose to twice the amount before injection. Smaller doses produced less marked or no effects. On discontinuing the injections glycosuria ceased after 2-3 days. In dogs with subtotal pancreatectomy, but with normal fasting blood sugar and no glycosuria smaller doses of extract raised the blood sugar (0.180-0.290 gm. %), produced polyuria and glycosuria (up to 1.1-4.5 gm. per kgm. per day), ketonuria increased considerably. After the injections were discontinued glycosuria persisted for several days up to 18 days after 4 days' treatment). Positive results were obtained in the 12 experiments performed. Muscle extract was injected in 7 experiments and only once was glycosuria obtained; also once in 5 experiments with thyroid extract and not in 2 experiments with posterior pituitary lobe extract and 2 with kidney extract. In hypophysectomized pancreatectomized dogs without diabetes the anterior lobe extract produces a severe diabetes; its action is therefore independent of the pancreas. In all the experiments in which determinations were made N-elimination increased slightly while the glycosuria produced by anterior pituitary extract lasted.—J. T. Lewis.

Hypophysis and thyroid. Effect of anterior lobe extract on blood iodine (Hypophyse et thyroïde. Action de l'extrait anté-hypophysaire sur l'iodémie). Houssay, B. A., P. Mazzocco and A. Biasotti, Compt, rend. Soc. de biol. **111**: 401. 1932.

In six dogs, intraperitoneal injections of anterior lobe extract resulted in increased blood iodine. If such treatment follows removal of one thyroid lobe, the augmentation of blood iodine, which normally follows lobectomy, is much increased. The anterior lobe of the hypophysis, therefore, plays an important part in iodine metabolism.—J. C. D.

Hypophysis and thyroid. Reactions of the thyroid of rats in parabiosis or when injected with anterior lobe hypophyseal extract (Hypophyse et thyroïde. Réaction de la thyroïde du Rat en parabiose ou injecté avec l'extrait anté-hypophysaire). Houssay, B. A., Compt. rend. Soc. de biol. **111**: 459. 1932.

Anterior lobe pituitary extract when injected did not increase the weight of the thyroid in rats and produced signs of histological overactivity only after very large doses. This is in spite of the fact that it produced a hyperfunction as shown by the animal's increased susceptibility to anoxemia. The thyroid of a normal rat united parabiotically with a thyroidectomized animal was not modified. The rat is a species in which the thyroid is not sensitive to overdoses of anterior lobe extract. The numbers used in these experiments are not given.
—J. C. D.

The administration of drugs into the cerebral ventricle of monkeys: pituitrin, certain pituitary fractions, pitressin, pitocin, histamine, acetyl choline and pilocarpine. Light, R. U. and S. M. Bysshe, J. Pharmacol. & Exper. Therap. **47**: 17. 1933.

An investigation of the nature of certain observations made by Cushing after the injection of pituitrin into the cerebral ventricles of human subjects

which lead to the assumption of a "parasympathetic center" in the walls of the third ventricle. Monkeys (Cercocebris aethrops) were used because of similarity of the brain to that of the human. One cubic centimeter of fluid was injected into the lateral ventricle. Under nembutal anesthesia trephine openings were made several days before the experiment. Six aminals were used for "pituitrin (S)" (Parke, Davis & Company). Vasodilatation of oral mucous membrane occurred in 30 to 40 seconds after cerebral injection, whereas absorption into the blood stream did not take place for 3 to 5 minutes. All fractions containing 20 or more pressor units per cc. gave the same response. Fractions containing less than one pressor unit gave no reaction when injected intraventricularly. Depressant drugs did not produce the flushing effect. Histamine tended to produce blanching.—C. I. R.

Changes in the oestrus cycle following semi-spaying (Troubles du cycle sexuel consécutifs a l'intervention ovarienne). Lipschütz, A. and B. Osnovikoff.

Activation of the anterior lobe of the hypophysis following semi-spaying (Activation de la préhypophyse par intervention ovarienne). Lipschütz, A., compt. rend. Soc. de biol. **111:** 350; 352. 1932.

In 14 guinea pigs, one ovary was removed completely together with the lower pole of the other. In many cases the animals showed disturbances characterized by prolongation of the active phases of oestrus, enlarged uterus, mammary gland, and extensive luteinization of the ovarian remnant. These resembled the condition found in an intact female parabiotically united with a castrated one. It was found that if portions of the anterior lobe from these semi-spayed females is injected into immature rats, the appearance of the first oestrus is much hastened: more so than if pituitary material from normal females is used. This indicates a higher content of prolan A in the semi-spayed animals and suggests that the increased amount of prolan A acting on the small remnant of ovarian material is the determining factor in the changes seen.—J. C. D.

The anterior lobe of the pituitary gland and iodine content of the thyroid gland. Loeser, A., Arch. f. exper. Path. u. Pharmakol. **163:** 530. 1931.

The author studied the effect of intraperitoneal injections of saline suspensions of acetone-dried anterior pituitary gland substance upon the total iodine content of the thyroid glands of young dogs. As controls he used the thyroid glands of normal dogs, which did not receive any injections and also the gland of one dog which had been injected with 5.0 grams of acetone-dried liver substance in saline suspension; and the thyroid of another dog which had received injections of saline suspensions of acetone-dried anterior pituitary gland substance which had been inactivated by boiling. Total iodine determinations were made by the method of Kuhn and Loeser, which is described in the paper. No attempts were made to determine separately the inorganic and organic iodine fractions. The author concludes that the injection of anterior pituitary suspension causes almost a total loss of the iodine in the thyroid gland. There was no diminution in the total iodine content of either the thyroid gland of the dog which had been injected with inactivated anterior pituitary gland suspensions or in the gland of the animal which had been injected with a suspension of dried liver substance.—Walter J. Siebert.

Effect of fats and extract of the anterior lobe of the hypophysis on the liver glycogen of rats treated with thyroid (Action des graisses et de l'extrait antéhypophysaire sur le glycogené hépatique des Rats traités par la thyroide). Magistris, H., Compt. rend. Soc. de biol. **111:** 397. 1932.

Eight rats were given thyroid powder for 4 days with their regular food. Six of these received in addition large amounts of fat. Ten other rats were similarly treated except that injections of a special extract of pituitary were substituted for the feeding of fat. Examination of the livers showed that the administration of fat permitted the storage of glycogen in spite of the thyroid treatment, which in control animals eliminated the liver glycogen. The hypophyseal extract had a similar effect on the formation of glycogen. It appears then that fat in the diet decreases the use of glycogen by stimulating the hypophysis. Directions for preparation of the extract are given.—J. C. D.

Effect of castration on the sex action of the toad's hypophysis (Rôle de la castration sur l'action sexuelle de l'hypophyse du Crapaud). Novelli, A., Compt. rend. Soc. de biol. **111:** 476. 1932.

The oxytocic power and the power to stimulate egg laying was not increased in the hypophyses of male toads following castration.—J. C. D.

Influence of castration on the sexual function of the pituitary (Influencia de la castración sobre la acción sexual de la hipófisis del sapo). Novelli, A., Rev. Soc. argent. de biol. **8:** 459. 1932.

Male toads (Bufo arenarum, Hens) weighing 100 to 130 gm. were castrated; 30, 60 and 90 days later they were killed (8 to 13 animals in each batch). The anterior and posterior pituitary lobes were weighed and no significant difference found compared with that of normal controls kept in identical conditions. The oxytocic power of the posterior lobe, determined on the isolated guinea pig uterus according to Burn and Dale's method, was the same in castrates and controls. The capacity to produce ovulation in female toads found in the anterior lobe was the same in castrates and controls.—J. T. Lewis.

Use of pyramidon in diabetes insipidus (Pyramidon beim Diabetes insipidus). Scherf, D., Wien. Arch. f. inn. Med. **22:** 457. 1932.

The use of large (2-3 gm.) doses of pyramidon daily results in a marked lessening of thirst and a definite diminution of diuresis in true cases of diabetes insipidus. The activity is diminished by continuing it for several days, but after stopping treatment for a few days the original effect is noted when the drug is again administered. Luminal does not give the same action. The intra-muscular use is also advised for other ills where thirst is a prominent symptom. The method and point of action are not to be explained as yet.
—R. A. Phillips.

The young cock as a test animal for the gonadotropic hormone of the anterior hypophysis (Le Coq impubère comme test de l'hormone gonadotrope préhypophysaire). Schockaert, J. Compt. rend. Soc. de biol. **111:** 1095. 1932.

Hypophyseal extracts injected into young cocks stimulated the growth of the comb and of the testis itself. Enlargement of the latter was due to rapid maturing of the seminiferous tubules.—J. C. D.

Specific action of beef anterior pituitary extracts upon the weight of the thymus of young duck (Action spécifique des extraits préhypophysaires de boeuf sur le poids du thymus du jeune canard). Schockaert, J., Soc. belge de Biologie, **105:** 226. 1930. Abst., Rev. belge sc. med. **3:** 1098.

The injection of anterior lobe pituitary extracts into ducks causes a marked decrease in the weight of the thymus. This decrease cannot be obtained by the injection of liver extract, lactalbumin, or oil of turpentine. It is a specific action of the anterior lobe pituitary extract upon the thymus and is caused by a quick increase of thyroid activity.—Translated by J. Gagnon.

Action of anterior lobe pituitary substances of mammals upon the testicle of the young duck (Action de substances préhypophysaires de mammifères sur le testicule du canard impubère). Schockaert, J., Soc. belge de Biologie, **108:** 429. 1931. Abst., Rev. belge sc. med. **3:** 1099.

The injection of hypophyseal extract into young ducks causes a considerable increase in the weight of the testicles. There is found microscopically the beginning of a very premature spermatogenesis taking place in the foetal testicles. Freshly examined ground testicles have shown numerous moving sperms. The interstitial tissue of ducks is not affected by injections of hypophyseal extracts.—Translated by J. Gagnon.

Influence of anterior pituitary substances on the total iodine content of the thyroid gland in the young duck. Schockaert, J. A. and G. L. Foster, J. Biol. Chem. **95:** 89. 1932.

The treatment of young male ducks with a fresh saline emulsion of beef anterior pituitary induced a rapid drop in the total iodine content of the thy-

roid gland. The total iodine content was as low after a week as after 5 weeks of treatment (one-tenth to one-twentieth of the normal). The percentage of iodine continued to drop more and more as the glands underwent marked hypertrophy and hyperplasia. The anterior pituitary fraction which contains the growth hormone also possesses this thyrotropic action.

—Authors' Summary.

Basal metabolism after KI with acid extract of anterior pituitary glands, pituitary tablets and with thyroid. Siebert, W. J. and E. W. Thurston, Proc. Soc. Exper. Biol. & Med. **29:** 652. 1932.

Guinea pigs injected daily with acid extract of beef anterior lobe show a marked rise in the basal metabolic rate (maximum—60%) within 12 days. If potassium iodide is fed to such animals, no significant rise occurs. When Armour anterior pituitary tablets were fed to guinea pigs there was an increased metabolic rate regardless of the concomitant administration of KI. Likewise thyroid substance caused an increased metabolic rate which was not influenced by KI finding.—M. O. L.

Further observations on the gonad-stimulating principle of the anterior lobe of the pituitary body. Van Dyke, H. B. and Zonja Wallen-Lawrence, J. Pharmacol. & Exper. Therap. **47:** 163. 1933.

A study of properties and assay for the details of which the original article should be consulted. The methods were unable to separate follicle-stimulating and luteinizing fractions.—C. I. R.

Influence of insulin on the nitrogen equilibrium in normal dogs (Effet de l'insuline sur l'équilibre azoté chez le Chien normal). Aubertin, E. and J. Mollaret, Compt. rend. Soc. de biol. **111:** 177. 1932.

Six normal dogs in nitrogen balance were given varying doses of insulin over considerable periods. It was found that insulin by increasing sugar consumption depleted the carbohydrate reserve of the body. If this was not made good by carbohydrate intake, there was an increased output of nitrogen. The fact that this effect is secondary and dependent on the carbohydrate available explains the conflicting results obtained by previous authors.—J. C. D.

Observations on effect of insulin in thin persons. Blotner, H., J. A. M. A. **100:** 88. 1933. Abst., A. M. A.

The author presents a clinical study of the effect of the subcutaneous administration of insulin in 19 healthy thin persons. Ten units of insulin, three times a day, was the standard dosage of insulin used, a few patients taking somewhat more or less than this amount, and a liberal diet was employed uniformly. After insulin injections were started, the patients gained weight rapidly and immediately. The increase in weight tended to become less marked as the weight approached the standard normal weight. In 13 cases after the omission of insulin the weight remained either constant or continued to increase during periods of subsequent observation, which varied from six weeks to fourteen months. Two patients lost 8 and 5 pounds (3.6 and 2.3 Kg.) of the gained weight within six months of the omission of insulin. Insulin appeared to act as an admirable tonic, all the individuals receiving it feeling much stronger and more active than they had felt previously. Mild hypoglycemic reactions occurred rarely. Local skin hypersensitiveness to insulin appeared in six cases. This finding is striking as compared with the rarity with which skin hypersensitiveness to insulin is seen in diabetic patients receiving the drug. There were no other untoward symptoms. The author believes that the gain in weight in thin persons taking insulin is probably due to an increased intake, better digestion and increased assimilation of food. The increase in weight does not appear to be due to water retention, as may occur in certain diabetic patients taking insulin. The relation between the fluid intake and output during and after the use of insulin was not abnormal, nor did diuresis develop after the omission of insulin. That insulin increases the appetite and produces an increased ingestion of food is suggested by a study of the nitrogen excretion in the urine. In the cases studied, the nitrogen excretion rose con-

siderably during the period of insulin therapy and then decreased after its omission to near the previous level. That insulin may increase the absorption and assimilation of food is suggested by a study of phenolsulphonphthalein excretion during the treatment. There was a uniform decrease of from 8 to 27% in the excretion in the urine of intramuscularly injected phenolsulphonphthalein during the period of insulin treatment and a return to the original level after the omission of insulin. This was possibly due to an increased excretion of phenolsulphonphthalein in the bile as a result of the stimulation of the flow of bile by insulin, and since the flow of pancreatic juice is similarly stimulated by insulin it is reasonable to assume that increased absorption of food may occur from its employment. That insulin serves as an admirable tonic physiologically as well as psychologically is suggested by a study of the plasma protein concentration, the red blood count and the circulating blood volume of persons receiving insulin. The plasma protein concentration tended to increase during and after the period of insulin administration. The red blood count showed an average uniform increase of approximately 400,000 red cells, which usually persisted after the omission of insulin. The blood volume also increased perceptibly during or shortly after the use of insulin. The basal metabolic rate was unaffected or possibly tended to show a slight decrease during or after insulin therapy. These data record evidence to explain some of the beneficial clinical results that may be obtained with insulin in certain conditions other than diabetes. Because of its varying action on different tissues, insulin may be of considerable value in the management of properly selected cases in which it is desirable to bring about gain in weight. The use of insulin for this purpose appears to be rational and is a simple and safe form of therapy.

Effect of a liver extract on blood sugar and respiratory quotient in diabetes. Bowen, B. D. and Grace E. Sly, Proc. Soc. Exper. Biol. & Med. **29**: 593. 1932.

The effect of liver extract on the respiratory quotient and the blood and urine sugar was studied in 2 diabetic patients. The effect of whole liver was studied in one patient. There was no evidence that either had a favorable influence on the diabetes.—Authors' Summary.

The use of insulin for the relief of symptoms following the sudden withdrawal of morphine (Insulin zur Bekämpfung der Abstinenzerscheinungen bei plötzlichen Morphiumentzug). Braun, F. Schweiz. Arch. f. Neurol. u. Psychiat. **27**: 226. 1931. Abst. Arch. Neurol. & Psychiat. **28**: 1932.

The beneficial results of treatment for morphinism with insulin, as originally reported by Sakel, find confirmation in 6 cases of rather severe addiction included in the present contribution. Braun's experience differs from Sakel's only so far as he found that sedatives in the form of scopolamine and barbital preparations were desirable adjuvants to the new form of treatment, and that the early withdrawal symptoms were not relieved to the degree reported by the latter. The symptoms were never so severe as to necessitate a cessation of treatment, however, and were of very short duration, becoming markedly ameliorated within three or four days. Some of Braun's patients who had previously been subjected to sudden withdrawal testified to the relative mildness of the symptoms in contrast to their former experiences. In each of the 6 cases, morphine was completely withdrawn and insulin was administered whenever the patient became restless, since it invariably exerted a marked sedative effect. The treatment was usually continued for 7 days, the daily dose of insulin ranging from 20 to 100 units. Solutions of sugar were not given until after the disappearance of the acute withdrawal symptoms. Following the disappearance of these symptoms the appetite quickly returned, the general appearance showed a marked change for the better and the patient became cheerful, usually evincing a desire to get to work. In every case the patient was highly gratified with the results of treatment, since the craving for morphine had been removed with a minimum of discomfort. As the author expresses it, a complete change of heart (Umstimmung) had occurred. Blood sugar determinations and other metabolic studies were not carried out. In discussing his results, Braun expresses the belief that although insulin might serve to replace the stimulating action of morphine on the parasympathetic nervous system, the metabolic changes effected by its use were the more essential.

The Mikulicz syndrome in diabetes mellitus. A contribution to the problem of the internal secretion of the salivary glands (Mikuliczuv syndrom u uplavice cukrove Prispevek k problemu vnitrni sekrece slinnych zlaz). Charvát, J., Casop. lék. česk. **5**: 1. 1932.

Three cases of mild diabetes are described. At the beginning of the disease there was painless, non-inflammatory, symmetrical swelling of the salivary glands lasting from 6 months to three years. Insulin treatment in one case and dietetic treatment in another diminished the swelling in the glands. Treatment in the third case was not completed at the time of the report.—M. O. L.

Absorption of insulin by nasal mucous membrane. Collens, W. S. and M. A. Goldzieher, Proc. Soc. Exper. Biol. & Med. **29**: 756. 1932.

The authors describe a procedure of administering insulin by nose which produces a drop in blood sugar resembling that obtained by subcutaneous injection. The method is based upon the principle of increasing the permeability of a membrane, free from inactivating ferments, by heat and weak acids, and lowering the surface tension of the insulin with the use of saponin. Thus the nose is irrigated with normal saline, pH 4 at 45 C. Then an insulin saponin solution at 50 C. is sprayed into the nose with an atomizer. A critical discussion of the literature on peroral insulin is presented.—W. S. Collens.

The absorption of insulin from the gastro-intestinal tract. Eaton, A. G. and J. R. Murlin, Am. J. Physiol. **101**: 31. 1932.

Totally depancreatized dogs are able to absorb considerable insulin when given with calcium lactate and sodium bicarbonate. The blood sugar falls 40 to 95 mg. %, the respiratory quotient rises and the urine usually becomes sugar-free for 4 to 8 hours after administration. The calcium lactate and sodium bicarbonate are believed to act as buffers, removing the free hydrochloric acid from the stomach and protecting the insulin from destruction by pepsin. When pancreatin is given with the food, the absorption is much less. A preliminary trial on three human diabetics showed a fall in blood sugar of about 60 mg. % in one case, and none in the others.—Authors' Abst.

A disturbance of the blood sugar regulation in individuals with an hereditary diabetic tendency (Über eine Störung der Blutzuckerregulation bei familiärer diabetischer Belastung). Flaum, E. and A. Schlesinger, Wein. Arch. f. inn. Med. **22**: 131. 1932.

The authors report observations on 31 individuals who are considered predisposed to diabetes because after administering 100 gm. dextrose to them by mouth there is a secondary increase of the blood sugar usually at least 60 minutes after the primary rise although in some cases an irregular plateau is found. They align their results with the explanations of v. Noorden and Lichtwitz concerning the production of pancreatic-hormone in cases of endogenous obesity. Anamnesia is also reported in some of their cases as a symptom.
—R. A. Phillips.

Glucose utilization by brain. Gerard, R. W. and R. J. Schachter, Proc. Soc. Exper. Biol. & Med. **29**: 525. 1932.

The metabolism of the brain, as estimated by the glucose taken from blood in passing through it, is in agreement with that determined by analogous studies of oxygen and carbon dioxide changes. Brain metabolism so estimated is at least 20 times as intense as that of resting muscle. This average does not differentiate the higher respiration of gray matter from white, the large amount of non-neural elements, and similar factors tending to dilute a much higher value for the nerve cells proper. Insulin does not uniquely influence brain sugar utilization.—Authors' Summary.

The purification and some properties of insulin. Gerlough, T. D. and R. W. Bates, J. Pharmacol. & Exper. Therap. **45**: 19. 1932.

Commercial insulin was further purified by fractional precipitation with 70% alcohol at pH 5.4-5.8 from systems of low salt content to yield products of very high potency, viz., 22 to 27 units per mg. These products, which were essentially equal in potency to crystalline insulin, contained from less than 0.1

to 0.56% tryptophane. Tryptophane was absent in crystalline insulin. Neutral salts increased the solubility of insulin in alcohol. Sulphates shifted the pH of minimum solubility in alcohol from the true iso-electric point to a more acid region. Chlorides and acetates did not materially alter the pH of minimum solubility. Relatively high concentrations of neutral salts increased the solubility of insulin at its iso-electric point in water sufficiently to permit their use as crystallizing solvents. Insulin was crystallized from (a) the solvents salts—NaCl, Na_2SO_4, $(NH_4)_2SO_4$, NaH_2PO_4-Na_2HPO_4, and from systems which contained organic solvents, viz., (b) brucine-pyridine-ammonium acetate (Abel), (c) 10-20% glycerol plus ammonium acetate and (d) 60% alcohol containing a small amount of NaCl. Of all the crystallizing solvents used Abel's was in general the most satisfactory. All crystals prepared by various methods possessed essentially the same potency per mg. Two forms of crystals were observed which confirmed the findings of Abel. Crystals were also obtained from an insulin solution which had been previously coagulated in dilute H_2SO_4 by boiling at 100° C. and then reversed with NaOH. The influence of pH, purity, HcHO and temperature on the rate of coagulation in dilute H_2SO_4 was studied in detail. Between pH 2.6 and 3.3 coagulation at 100° C. proceeded very slowly but increased rapidly with increasing hydrogen ion concentration. Highly potent preparations coagulated rapidly. The addition of dark colored inert protein impurities retarded their coagulation. HcHo also had a marked retarding effect. The rate of coagulation conformed to that calculated for a first order reaction. It was predicted from viscosity measurements that the probable molecular weight of insulin should be 40,000 to 50,000.

—T. D. Gerlough.

Paradoxical insulin action (Seltene Insulineffekte). Gorlitzer, V., Wien. Arch. f. inn. Med. **22**: 141. 1932.

The water balance in two cases of diabetes mellitus and of one of renal diabetes is discussed with relation to the paradoxical effects of insulin and the action of other glandular extracts with which these cases were treated.

—R. A. Phillips.

The influence of insulin on gastric activity (Der Einfluss des Insulins auf die Magentätigkeit). Heller, H., Ztschr. f. d. ges. exper. Med. **79**: 607. 1931.

The author studied the influence of the injection of insulin in doses of 15 to 30 units upon the secretory activity of the stomach. The stomach was empty at the time of each injection. He found that gastric secretion as indicated by the acid content was augmented and that this occurred 1 to 1½ hours after the administration of insulin. These values were highest in individuals with gastric ulcer and those of the ulcer habitus. Insulin was without effect in cases of anacidity associated with pernicious anemia or cancer. He reports that insulin is of value in revealing false anacidity. The author believes this action of insulin is due to the resulting hypoglycemia. In diabetes mellitus the effects are variable depending upon the sugar content of the blood. Also, he finds atropin to inhibit this action of insulin upon the stomach.—S. Shapiro.

Contribution to the knowledge of the mechanism of equilibrium of the internal secretions. The effect of tobacco-smoking on blood sugar (Beitrag zur Kenntnis des innersekretorischen Gleichgewichtmechanismus. Die Einwirkung des Tabakrauchens aug den Blutzucker). Lundberg, E. and S. Thyselius-Lundberg, Acta med. Scandinav. (Suppl.) **38**: Pp. 1. 1931.

The purpose of these investigations was to determine the immediate effect of smoking on the blood-sugar under varying conditions and to correlate the results obtained with the mechanism of equilibrium of the internal secretions. For the direct effect of smoking on the blood-sugar, the tests were conducted on both healthy individuals and those affected with diabetes. Cigarettes or cigarettes and cigars were used for the experiments. The tests were either continuous or intermittent. The quantity of tobacco in every case was varied between 0.45 and 1.1 gram. Smokers and non-smokers of both sexes were submitted to the tests. Hagedorn's method was used for the determination of blood-sugar. Immediately after smoking began, the blood-sugar rises quickly to a considerable height which is about 50% higher than the starting value. The maximum generally is reached during the smoking. Afterwards the blood-sugar decreases, but more slowly than it increased and usually within half an

hour it is normal again. Such reactions were not observed when nicotin-free tobacco was used. It is probable that this phenomenon is due to increased secretion of adrenaline. The maximal increase of blood-sugar seems to depend upon the equilibrium of the internal secretions of the individuals in such manner that the maximal value is lower when complete equilibrium prevails and higher when some factors disturb the equilibrium. For example, the consumption of one cigarette is a disturbing factor and as a consequence the individual responds with an increase in blood-sugar at the next smoking. In the same way the presence of diabetic disturbances of the metabolism is manifested by the fact that it evokes a stronger reaction of blood-sugar to nicotine than in the case of healthy persons. In the course of treatment of diabetics the state of the actual disturbances of the metabolism can be followed up generally by the maximal values of reaction to nicotine. While the patient's metabolic disturbances are characterized by segregation of sugar and acetone, the individual will respond with a stronger maximal reaction to smoking than when these products of diabetic segregations have disappeared. The above investigations also demonstrate the necessity of thoughtful consideration, when, if ever, diabetic patients should be permitted to smoke.—G. L. Banay.

Treatment of the same diabetic patient with widely varying diets. Strouse, S. and S. Soskin, Tr. A. Am. Physicians, **47**: 317. 1932.

In all dietetic therapy our goal should be as near an approach to the normal diet as is consistent with the underlying pathological conditions. The authors' experiments reveal no reason for imposing markedly abnormal or disproportionate dietary mixtures upon the diabetic patient. The diabetic manifestations of many patients can be equally well controlled on widely varying mixtures. The dietary objective in the insulin-treated diabetic should be to meet the demands of an individual leading a full normal life. In most instances of uncomplicated diabetes this can be accomplished by a comparatively simple study of the individual patient's needs and desires and the demands of his diabetes. The problem of feeding insulin-treated diabetic patients does not involve the application of formulae or strict adherence to any particular type of diet. Since these patients do equally well on widely varying diets, the question involved is not one of high fat or high carbohydrate but of a well-balanced, comparatively normal regime.—I. B.

Studies on the regulation of calcium in rabbits. Effect of the thyroid and parathyroids (Recherches sur la régulation de la calcémie chez le Lapin. Influence de l'appareil thyro-parathyroïdien). Baudouin, A., E. Azerad and J. Lewin, Compt. rend. Soc. de biol. **111**: 295. 1932.

Twenty-one rabbits were used. Intravenous injection of sodium oxalate reduced the blood calcium, whether the parathyroids were present or not.
—J. C. D.

Studies on calcium; effective dose of calcium gluconate subcutaneously administered in completely parathyroidectomized dogs. Bourns, E., Proc. Soc. Exper. Biol. & Med. **29**: 546. 1932.

Five thyroparathyroidectomized dogs remained in a normal state of health without evincing tetany when given subcutaneously 1.5 cc. of a 10% solution of calcium gluconate per kilo of body weight daily even when on a fairly high protein intake.—M. O. L.

Osseous changes in hyperparathyroidism. Campo, J. D., J. A. M. A. **99**: 1913. 1932. Abst., A. M. A.

The coexistence of changes in bone with disease of the parathyroids has long been noted. The predominating osseous changes are generalized atrophy and multiple cystic lesion. The author noted that when roentgenograms from cases of hyperparathyroidism are compared, certain fundamental and predominating structural changes are revealed in the osseous system which are so strikingly similar and constant that they suggest a characteristic roentgenographic picture for hyperparathyroidism. Roentgenologically, the fundamental skeletal change (decalcification) is revealed in the majority of cases as uniform, miliary, granular osteoporosis. This peculiar form of mottled atrophy is distinct from the ordinary type seen in osteoporosis associated with acute and

chronic disease of bone and neurotrophic conditions. In the author's experience there was no other generalized skeletal lesion which exactly simulated the miliary mottling and granular appearance of the bone in hyperparathyroidism, and such an appearance seems to be characteristic of this condition. The change is best exhibited in flat bones, especially the calvarium. Also, the resorption of calcium causes the bone trabeculae to become indistinct in outline and the cortical bone to be thinned so that in early cases the bones have a homogeneous ground-glass appearance. In some regions the decalcification progresses to produce multiple cystic areas of varying size, which may be found within the medullary portion or below the periosteum. The jaws, pelvis, long bones, ribs and metatarsal and metacarpal bones are favorite sites for such changes. The subperiosteal areas of resorption are especially well shown at the ends of long bones and in the phalanges. Cysts may reach a large size and become the site of pathologic fractures. Because the bones are soft, bowing, kyphosis, narrowing of the pelvis and coxa vara are common. The author describes in detail the changes observed in the skull, long bones, spinal column, pelvis, hands and feet.

Heterotopic bone formation in thyroparathyroidectomized dogs. Dragstedt, C. A. and J. E. Kearns, Am. J. Physiol. **100**: 262. 1932.

Heterotopic bone formation occurred in 7 thyroparathyroidectomized dogs receiving adequate calcium therapy in (a) fascial transplants in the wall of the urinary bladder, and in (b) the cysts formed by stitching the urinary bladder musoca to the rectus fascia. Such heterotopic bone formation occurred to a slighter extent in 18 thyroparathyroidectomized dogs receiving minimal calcium therapy.—R. G. H.

Acute hypercalcemia; report of a case. Lowenburg, H. and T. M. Ginsburg, J. A. M. A. **99**: 1166. 1932.

Lowenburg and Ginsburg report the case of a white male five years old who by accident received 1 vial (5 cc. or 100 units) instead of 1 cc. of parathormone daily for six days, in the course of treatment for purpura hemorrhagica. Symptoms consisted at first of increasingly severe vomiting. In the course of three days the patient became listless then soon showed general physical depression. These symptoms increased in severity until by the fifth day the condition was considered critical, there being great apathy, lethargy, and listlessness, with an inability to sit up spontaneously. The knee jerks were absent. The patient ran a high, irregular fever. The condition was recognized on the sixth day when an immediate blood calcium determination was made, showing 19.6 mg. per 100 cc. Serum phosphorus was 4.4 mg. per 100 cc. (Serum calcium two days before parathormone was started was 10.2 mg. per 100 cc.) Treatment consisted of continuous venoclysis of saline. The next day the condition had markedly improved and by the fourth day the symptomatology and blood picture had returned to normal and remained so. X-ray observation of the long bones on the seventh day disclosed no absorptive changes. It is suggested that in future the administration of calcium constitute a part of the treatment because the presence of the hormone in excess might ortherwise lead to absorption of calcium from the bones in order to maintain the high blood level.—Authors' Abst.

Tetany. Meakins, J. C., M. Clin. North America, **16**: 688. 1932.

This is a survey of present knowledge on the subject with presentation of three cases. The first was that of a rachitic child, healthy in appearance but subject to convulsions, which improved on a high calcium diet and high vitamin intake. The second case was that of osteomalacia in a woman who had had a child one year previously and nursed it for eleven months. She was placed on an antirachitic diet rich in vitamin D with parathormone and calacium lactate. The tetany was soon controlled, although during intermittent attacks of diarrhea it would return. The condition was also improved by an artificial menopause produced by x-rays. Attention is called to the tetanic condition in cattle known as "milk fever," and to a condition formerly occurring in lactating women, both of which are due to depletion of the calcium in the bones due to lactation. The third case reported showed development of tetany after subtotal thyroidectomy. Calcium lactate in combination with parathormone gave encouraging results. On Jan. 16, 1930, the parathyriod glands of a stillborn baby were transplanted into the patient's rectus muscle. Attacks continued

for 15 months at irregular intervals, then became less severe and much less frequent. The blood calcium had become normal and the patient had had no attack for nearly a year.

Clinical and experimental observations upon the heart in hyperthyroidism. Andrus, E. C., Tr. A. Am. Physicians, **47**: 47. 1932.

In a series of 200 cases of hyperthyroidism congestive heart failure occurred in 18.5%. The average duration of symptoms was greater in cases with myocardial insufficiency. Its incidence increased in the age decades above 40 years, and was most common in any age group in association with other preexistent factors which tend to diminish cardiac reserve such as rheumatic heart disease, hyperthyroidism, arteriosclerosis, or, more rarely, syphilitic heart disease. It also seems pertinent to call attention to the frequency of established auricular fibrillation among the cases of congestive heart failure. A totally irregular ventricular rhythm presents a serious handicap to an already overburdened circulation. In a series of observations it has been impossible to demonstrate any direct effect of thyroxine upon the isolated heart in vitro. Neither the perfused hearts of rabbits nor their auricles suspended in oxygenated Ringer-Locke's solution were affected by exposure to thyroxine in concentrations up to 1 to 25,000 for as long as 24 hours. Also, it is impossible to reproduce Graves' disease in animals by means of repeated injections of thyroxine. However, the injection of thyroxine into a rabbit is followed by a series of events which are homologous with the signs and symptoms of hyperthyroidism in man. During the first 18 to 24 hours no change may be noted. This "latent period" appears to be characteristic of the action of thyroxine. It finds a clinical counterpart in the interval elapsing between the partial removal of the overfunctioning thyroid gland from a patient with Graves' disease and the "postoperative storm" which frequently follows. By the end of 36 hours the animal becomes more than usually responsive to stimuli. Appetite and thirst increase; the basal metabolic rate is augmented. The heart rate is unusually rapid. If the injection is not repeated these manifestations disappear within the succeeding two weeks. If the thyroxine be continued the animal loses weight, becomes weak and fatigues rapidly upon the slightest exertion, and finally dies in a state of emaciation and exhaustion. Observations made upon certain physiological properties of the hearts removed from thyroxinized animals at the height of the thyroxine effect indicate that the hearts, or auricles, of such animals continue to beat, after isolation, at a rate conspiculously more rapid than those of normal controls. Moreover, this tachycardia characteristically persists for hours, tending to decrease with time far less than the rate of spontaneous rhythm of the isolated normal heart. This is in contrast with the tachycardia produced with large doses of atropin or adrenaline, which abates rapidly following isolation of the heart. The addition of adrenaline to the bath in which are suspended the auricles from normal and thyroxinized rabbits brings about the same per cent acceleration in both, i.e., a greater absolute acceleration in those of the thyroxinized animals. By direct volumetric measurements it has been shown that isolated auricles from small guinea-pigs to which thyroxine had been administered consumed from 7 to 20% more oxygen per gram of tissue than auricles or similar hearts from normal animals. Chemical estimations have been made of certain constituents of cardiac and skeletal muscle from normal rabbits and from those which had received thyroxine with results indicating that there is a profound displacement of the carbohydrate metabolism of these tissues to the extent that their glycogen content is conspicuously depleted. In a proportion of instances this is accompanied by an increase in the concentration of lactic acid. Such results appear to indicate that the myocardium shares in the metabolic upheaval characteristic of hyperthyroidism. Far from justifying any inference that the heart is uniquely poisoned by the thyroid secretion they suggest that the metabolism of cardiac muscle is augmented as is that of skeletal muscle and of the body tissues generally. The increased circulatory demands created by any conditions which increase metabolism increase the work of the heart. In hyperthyroidism the metabolic alterations in the myocardial tissue render this work abnormally expensive. These two factors combine in all cases, varying only in duration and degree, to bring to the fore the cardiac manifestations of the disease. Their effect may be determined by the soil upon which they are implanted. In individuals whose circulatory reserve has been diminished by age, or by organic cardiac disease, they may result in cardiac failure. Presumably this may develop when the load thrown upon the myocardium exceeds or approaches the limits set by its own metabolism.—I. B.

Plethoric and extremely obese thirteen-year-old child with arterial hypertension and hypothyroidism; discussion of endogenous and exogenous factors in obesity and of the methods for safe reduction of weight. Barker, L. F., Internat. Clin. **3**: 15. 1932.

The patient was a child of 13, weighing 222 pounds. She weighted 16 pounds at birth and 140 pounds at the age of ten. There was a family history of obesity on both sides, and the patient presented arterial hypertension and was regarded as showing hypothyroidism with her obesity. She was plethoric in type, with precocious sex development but no evidences of hypophyseal obesity, and a B.M.R. of 67% normal.—I. B.

The physiological activity of iodine in thyroglobulin. Barnes, B. O., Am. J. Physiol. **101**: 583. 1932.

By the use of pancreatin, thyroglobulin was split into an acid-soluble fraction and an acid-insoluble fraction. The iodine content of each fraction was about the same in some cases. The acid-soluble fraction caused a loss of weight in rats and rabbits. It does not cause elevation of body temperature, increase in basal metabolism or diarrhea. The acid-insoluble fraction caused much greater weight losses, severe diarrhea, elevation of body temperature, increased heart rate, rapid respiration, and a rise in basal metabolism. If artificial digestion has not destroyed any of the physiological activity, at least only half of the total iodine in the thyroid is combined with the active principle.

—Author's Summary.

Changes in sensitivity of the sympathetic by means of thyroxine (Erregbarkeitsanderung des Sympathikus durch Thyroxin). Bergwall, A. and G. Kuschinsky, Arch. f. exper. Path. u. Pharmakol. **162**: 169. 1931.

It was already known that thyroxine administration to thyroidectomized rabbits sensitizes the heart to adrenaline, and that there is evidence of sympathetic overactivity in Basedow's disease. These evidences of stimulation of the sympathetic by the thyroid led the author to investigate the possible effect of thyroxine upon the sensitivity of the rabbit's pupil to adrenaline. In preliminary experiments determination was made of the quantity of adrenaline administered intravenously necessary to produce the first photographically perceptible dilatation of the atropinized or sympathetic-denervated pupil. This threshold dose was in the neighborhood of 0.2 to 0.7 1000ths of a mg. of adrenaline per kg. It was found that the dose varied less in the same animal at different times than from animal to animal, and that its variability in the same animal could be completely suppressed by removal of the suprarenals. If the suprarenals were not removed, the administration of a total of 5 to 20 mg. of thyroxine over a period of 4 days or more led to an apparently significant rise in the threshold dose in 6 animals (pupil sensitivity decreased), and fall in 8 animals. Pupil denervation (sympathetic) increased the sensitiveness of the pupil to adrenaline, but did not modify the variability of its reaction to thyroxine. If, however, in such thyroxine treated animals, the sympathetic was then removed, an increased sensitiveness of the pupil to adrenaline was uncovered (4 animals). On the other hand, a continuous intravenous infusion of adrenaline of several minutes' duration given to 5 animals that had been treated with thyroxine and then suprarenalectomized, prevented the sensitizing effect of thyroxine from manifesting itself. A similar adrenaline infusion to otherwise untreated animals decreased the pupil sensitivity to independent adrenaline injection, and the higher the concentration of infusion the greater the dosage of the independent ardenaline injection necessary to elicit pupil dilatation. Insulin decreased the pupil sensitivity to adrenaline in 2 (?) animals. This effect was not seen after suprarenalectomy. Hyperventilation by artificial respiration decreased pupil sensitivity. This decrease in sensitivity was suppressed by removal of the suprarenals and again restored in these animals by continuous adrenaline infusion. The author concludes that thyroxine acts directly on the pupil to increase its reactivity to adrenaline, but by causing the suprarenals to maintain a higher concentration of adrenaline in the blood, thyroxine also acts to decrease the pupil sensitivity to adrenaline. The balance between these two mechanisms determines the net effect.—E. C. Albritton.

The identity of adenoma of the thyriod. Boyd, W., Tr. A. Am. Physicians, **47**: 268. 1932.

So-called adenomata of the thyroid, formed by stimulation of the entire gland or of certain areas, in the direction of hyperplasia or involution, and subsequent encapsulation of such areas by surrounding cells to form nodules, are not new growths or neoplasms in the true sense of the word. The condition is a nodular goiter rather than an adenomatous one. Adenomas or rather nodular lesions of the thyroid are divided into colloid and fetal forms. Histologically at first sight the difference between the two appears extreme but it is doubtful if it is really fundamental. In the colloid adenoma areas of budding and of degeneration can be detected, while in the fetal adenoma some areas may be characteristically colloid in type. We are ignorant with regard to the factors which determine whether the acini should become quiescent and distended with colloid or should show active evidence of proliferation and degeneration. No mention is made of toxic adenoma as the author does not touch on the relation of changes in thyroid structure to disturbances of function.—I. B.

Relation between myasthenia gravis and exophthalmic goiter. Cohen, S. J. and F. H. King, Arch. Neurol. & Psychiat. **28**: 1338. 1932.

A case of expohthalmic goiter with myasthenia gravis is reported. The heretofore reported cases of exophthalmic goiter with myasthenia gravis are reviewed. The cases of the combination of myasthenia gravis with exophthalmic goiter do not exhibit lesions of the brain or of the spinal cord. There is a similarity in the pathology, pathogenesis and endocrine dysfunction in exophthalmic goiter and myasthenia gravis. Attention is called to the beneficial effect of ephedrine in myasthenia gravis alone, as well as when it is complicated by exophthalmic goiter.—Authors' Summary.

Influence of hydric nourishment on body development and genesis of goiter and thyroid dysfunction. Colella, R., Riv. di pat. nerv. **37**: 355. 1931. Abst., Arch. Neurol. & Phychiat. **28**: 1202.

The author, who has investigated the origin of goiter and thyroid dysfunction from both a clinical and an experimental standpoint in relation to hydric nourishment, reaches the following conclusions: Goiter, bodily development and thyroid dysfunctions are directly correlated with the use of certain goiter-producing waters. The use of such water from birth and thereafter for a long time produces in mammals under experiment hypertrophy of the thyroid and morphologic changes of the body as represented by a retarded bodily development associated with a precocious somatopsychic development. The goiter-producing water produces in man an enlargement of the thyroid gland that occurs in endemic form among the population, and especially among the women. In the more advanced stage, from the simple hypertrophy of the thyroid the exophthalmic type of goiter may develop. Besides, other thyroid dysfunctions may be observed with particular reflection on the menstrual period, pregnancy and the menopause. It follows that simple goiter and its exophthalmic type (Flajani-Basedow disease) may represent the first, and the last link of a chain of intermediary pathologic conditions which seem to uphold the conception of unity of the so-called hyperthyroid syndromes. Various intermediate stages of such conditions may acquire a familial character, developing in various members of the family. The mental disturbances which may accompany the various types of exophthalmic goiter, and which in the typical form of the disease are represented by elementary mental disorders, involve more the emotional side of mental life. Rarely, typical manic or depressive attacks or acute confusional hallucinatory stages or schizophrenic manifestations, though atypical in type, occur. For the development of such mental conditions, however, the hydric factor is not the only one to be taken into consideration. Concerning the pathogenesis of the condition, the author believes the thyroid to be the fundamental element. In the thyroid infectious or toxic elements may determine the modification of the quality of the colloid substance, which, therefore, would influence abnormally the nerve tissue, especially of the sympathetic system. In regard to the active principle of the goiter-producing water, the author believes that it contains specific germs, or a toxic substance liberated by germs, which directly affect the thyroid tissue. The experiments of the author do not allow him to establish definitely the exact nature of the toxic or infectious agents. The hydric type of thyroid involvement is only one type of goiter-producing

condition, as the author believes that hypertrophy of the thyroid and exophthalmic goiter may be due to more than one pathogenic element. Along therapeutic lines, the author advises the removal of a certain group of waters which he has particularly studied and which he considers to be goiter-producing. He advises the use of opotherapy (serum of thyroidectomized animals), diathermy and galvanization of the thyroid, and finally radiothermy and surgical removal.

Blood iodine studies; the quantitative determination of the iodine content of blood. Davis, C. B. and C. M. Curtis, J. Lab. & Clin. Med. **18**: 24. 1932.

The method used for the quantitative determination of the blood iodine is difficult. It is best carried out in a laboratory used solely for that purpose and one in which no tincture of iodine or other volatile form of iodine is present. Such reagents used in the procedure as contain iodine should be handled with extreme care to prevent possible iodine contamination of the blood samples. With practice it proved to be possible to make duplicate determinations on blood samples containing 0.8 to 1.2 gamma with a variation between duplicates of about 0.05 gamma, or an error of from 6% to 8%.—I. B.

The effect of experimental hyperthyroidism on gastro-intestinal motility. Fetter, Dorothy and A. J. Carlson, Am. J. Physiol. **101**: 598. 1932.

Daily feeding of 0.4 gram per kilo body weight of desiccated thyroid per dog increased the activity of the empty stomach of dogs as shown by the type and height of the contractions of the empty stomach. After the thyroid feeding was discontinued there was a lowering of gastric activity, although in two months a return to the normal level was not observed in two dogs. During the period of thyroid feeding the emptying time of the stomach was decreased, and a barium meal passed more rapidly through the small intestine. After the administration of thyroid was stopped, the speed of the barium meal through the digestive tract returned to its former rate.—Authors' Summary.

Effect of induced hyperthyroidism on the gastro-intestinal motility of vagotomized dogs. Fetter, Dorothy, L. Barron and A. J. Carlson, Am. J. Physiol. **101**: 605. 1932.

Upon the administration of thyroid substance, 4 vagotomized dogs showed: (1) an increase in hunger contractions; (2) an increase in the speed with which a barium meal passed through the digestive tract, particularly the stomach and the small intestines.—Authors' Summary.

Hyperparathyroidism. Geddie, K. B. and J. de J. Pemberton, Ann. Surg. **92**: 202. 1930. Abst., J. Nerv. & Ment. Dis. **76**: 190.

A case of hyperparathyroidism in a young girl is described in which symptoms were due to excessive parathyroid secretion caused by a parathyroid adenoma. The symptoms and data include progressive weakness and loss of muscular tonus, attacks of abdominal pain and vomiting, anemia, polydipsia and polyuria, hypercalcemia and hypophosphatemia, and diffuse decalcification of the skeleton. The clinical features were reviewed and an attempt was made to rationalize and explain them on previously observed experimental, physiological, or pathological facts. Data concerning six other proved cases and three not proved by operation were gathered from the literature. The symptoms of this case differed from the other proved cases in that they were of shorter duration and that the chief complaints were referable exclusively to the gastro-intestinal and genito-urinary systems rather than to the osseous system. The surgical removal of the parathyroid tumor in the case reported was followed by marked relief from all symptoms.

Thyroid treatment before and during the fertile period and its influence upon the offspring (Schilddrüsenbehandlung vor und während der Tragperiode und deren Einfluss auf die Nachkommenschaft). Gudernatsch, F., Montaschr. f. Geburtsh. u. Gynäk. **88**: 161. 1931.

If the dosage of thyroid is too great the recognized symptoms of hyperthyroidism appear, emaciation, diarrhea, muscular weakness and, finally, cachexia causing death. The hair becomes yellowish, stands out straight, in many cases falls out in patches; in a word, the whole growth of hair becomes shabby.

(This agrees with the observations on birds.) If the dose was regulated so that the animals remained in comparatively good health the fur still became shabby and there were no offspring. Not one pairing of adult rats, both of which had thyroid treatment, showed any result after the rats had been brought together. Pregnancy appeared only after a long time for impregnation seemed to be possible only after several weeks had elapsed after the stopping of thyroid treatment. Where pregnancy was achieved the result was either abortion, or death of the young shortly after birth, or in very late pregnancies the young were inclined to be small. Although they were not especially weak, they were smaller than the young of normally fed rats.—J. Gagnon.

The significance of lymphatic tissue and adenoma-like areas in the thyriod gland. Himmelberger, L. R., Ann. Int. Med. **5**: 1404. 1932.

It has been shown that areas of lymphatic tissue occur in the thyroid gland in 2.8% of infants. This tissue is also found in 2% of thyroids from patients dying from diseases or accidents not involving the thyroid gland. Areas of lymphatic tissue occur in practically all thyroid glands removed surgically from cases of undoubted Graves' disease. The lesion described is not the result of a local inflammatory reaction. The presence of lymphatic tissue in infant and selected necropsy and specimens supports Warthin's contention of the existence of a "Graves' constitution," that exophthalmic goiter is the clinical manifestation of a congenital constitutional anomaly. Warthin's conclusion that this lesion is diagnostic for Graves' disease is vigorously supported. Adenomata have no causal relationship to the symptoms of thyroid disease since they occur with equal frequency in normal and pathological glands. The use of the term should be abandoned in connection with the clinical diagnosis of hyperthyroidism. A simple classification and diagnostic scheme of thyroid disease that is clinically and pathologically compatible is suggested.

—Author's Summary.

The modifications of the blood picture in the offspring of hyperthyroidized females (Le modificazione della crasi sangiugna nei figli di femmine ipertiroidizzate). Jedlowski, P., Boll. d. Soc. ital. di biol. sper. **6**: 1093. 1931.

Experiments were made on guinea-pigs and rabbits to determine the effect of experimental hyperthyroidism of the mothers upon the blood-picture of the young during the period of pregnancy and suckling. A group of pregnant guinea-pigs were subjected to moderate thyroid treatment by daily injections of ½-1 cc. of 5% thyroid extract for 20 days. The blood constitution of the young was examined six days after birth. A group of rabbits were similarly treated during the first 10 days of suckling. At the conclusion of the treatment the blood of the young was examined. Fifteen to 20 days later new counts were made to find out to what extent the previous modifications prevailed after the transmission of the thyroid hormone through the breasts had ceased. In 26 young guinea-pigs the average number of the red blood corpuscles was found to be about 6,150,000. In the control cases of similar age the mean rate was not more than 4,500,000. Because the transfer of the thyroid hormone through the breasts was checked by feeding of the young by unthyroidized females, so the increase of the red corpuscles is due exclusively to the thyroid treatment of the mothers and transmitted to the fetus by way of the placenta. In most cases the offspring showed a greater number of red corpuscles than the respective mothers. But the hyperglobulia did not last long. Fifteen to 20 days after birth no difference could be noted between the experimental animals and the control cases. The tests were conducted on 30 young rabbits. Comparing the control cases, the following changes were observed: slight increase of the red blood corpuscles, marked decrease of the leukocytes and, above all, a sharp rise of the reticulocytes. As regards the white-blood-corpuscle-formula, the decrease of the pseudoeosinophils was characteristic. This blood-picture is most clearly apparent during the period of suckling. As soon as the transmission of the thyroid hormone is stopped, the blood constitution returns to normal, excepting perhaps a mild leukopenia and a slight lymphocytosis which is more pronounced than in the control cases of the same age. The effect of the thyroid hormone upon the erythropoiesis is manifested mainly by a very great increase of the granulophilocytes and by an increase of the lymphocytes at the expense of the granulocytes.—G. L. Banay.

The characteristics of endemic cretinism in Pamir (Zur Charakteristik des endemischen Kretinismus im Pamir). Korovnikov, A., Wien. Arch. f. inn. Med. **22**: 85. 1932.

The paper is a description of the types of cretinism seen in Pamir with photographs and short protocols of typical individuals. No bibliography is included. Clinical findings noted included: erythrocytosis, relative and absolute lymphocytosis and eosinophilia, increased hemoglobin, hypotension and hypofunction of the heart with an increased heart size in relation to the size of the body.—R. A. Phillips.

Iodine question in Lettland in relation to goiter (Die Jodfrage in Lettland im Zusammenhange mit dem Kropfe). Kupzis, J., Ztschr. f. Hyg. u. Infektionskr. **113**: 551. 1932. Abst. Chem. Absts. **26**: 5317.

The iodine content of the soil depends upon the ease of leaching and the extent of pollution with animal and vegetable waste. Calcium, magnesium and iron and organic matter in drinking water do not affect goiter. The progress of goiter in Lettland and other countries can be explained by the replacing of iodine-rich Chile saltpeter with the iodine-poor calcium saltpeter, by the use of electricity in industry and the subsequent loss of smoke and coal and wood ash, the carrying of pure water from regions deficient in iodine and by the draining of bogs.

The stimulating action of anterior lobe hypophyseal extracts upon the thyroid gland (A propos de l'action stimulante des extraits préhypophysaires sur la thyroïde). Schockaert, J., Soc. belge de Biologie, **105**: 223. 1931. Abst., Rev. belge sc. med. **3**: 1098.

The injection of gland extracts other than anterior lobe of the hypophysis as well as the injection of lactalbumin, antitetanus serum, and oil of turpentine cause the same modifications of the thyroid gland as is caused by pituitary extracts although to a much less extent. This causes the specific action of pituitary extracts upon the thyroid to be regarded as doubtful.

—Translated by J. Gagnon.

Exophthalmos produced by injections of acid extract of anterior pituitary gland of cattle. Loeb, L. and Hilda Friedman, Proc. Soc. Exper. Biol. & Med. **29**: 648. 1932.

The administration of acid extracts of beef anterior pituitary gland to guinea pigs caused exophthalmos, in addition to other signs of marked thyroid overactivity which have been described before.—M. O. L.

Further studies on the etiology of goiter. The effect of cyanides. Marine, D. and E. J. Baumann, Tr. A. Am. Physicians, **47**: 260. 1932.

It has been shown by Webster and the authors that goitrogenic activity of cabbage varies seasonally. Iodine determinations showed that variations in quantity of iodine was not an important factor. It has also shown that steaming cabbage for an hour or more at 97 to 100 degrees Centigrade did not impair, and under certain conditions increased, its capacity to produce thyroid hyperplasia. Webster and Cipra showed that boiling finely hashed cabbage for 30 minutes at pH 3 (HCl) did not injure its goiter-producing capacity. Drying in a current of air, or in vacuo to a water content of less than 10% caused a complete loss of the goitrogenic agent; while removing 50 to 75% of the water content by drying proportionately reduced but did not completely remove the goiter-producing substance. On the other hand, removing 50 to 65% of the water from steamed cabbage in a wine press did not impair the goiter-producing capacity of the cabbage residue, while the press juice was entirely inactive. This residue (press cake) when washed with two or three volumes of water, was still active, showing that the goitrogenic agent is only slightly soluble in water. Acetone, alcohol, ether, and pentane extractions rendered the cabbage residue inactive. Ether extracts of fresh or steamed cabbage, fed with a standardized diet of oats and alfalfa hay produced hyperplasia. Cauliflower, brussels sprouts, kohlrabi, turnip, and rutabaga produced goiter when fed in the same caloric amounts as cabbage. Carrots, lettuce, and fresh alfalfa, fed in the corresponding caloric amounts, gave negative results. Mustard oils (isothiocyanates), such as abound in the Brassicae, were fed with

negative results. The corresponding nitriles were then tested. When acetonitrile was injected subcutaneously into prepubertal rabbits in doses of 0.1 cc. daily for three to four weeks a very striking thyroid hyperplasia was produced in animals maintained on a diet of alfalfa hay and oats. Feeding fresh green foods other than the Cruciferae prevented thyroid hyperplasia. Adult rabbits (over six months) tolerated larger doses but the thyroid hyperplasia was not so marked. Several of the nitriles and some inorganic cyanides have been tried and have this effect in greater or less degree. One can conclude that the thyroid hyperplasia is due to a cyanide and not to the radical with which it is combined. Neutralization of the thyroid action with sodium thiosulfate has failed. There is a very abrupt increase at puberty in the amount of acetonitrile a rabbit can tolerate and a decrease in the thyroid response. Sexual maturity appears to be somewhat hastened by prolonged acetonitrile administration. The reason is not clear. The exophthalmos that occurs is bilateral and chronic. So far only mild grades have been observed and mostly in males below the age of puberty. It has not been observed in rabbits in which the acetonitrile injections are begun after puberty. Once exophthalmos is produced it remains after sexual maturity if the cyanide injections are continued. About 80% of young rabbits have responded with significant thyroid hyperplasia in three to four weeks while perhaps 50 to 60% of young males develop tangible exophthalmos after varying lengths of time. The evidence suggests that the thyroid hormone and an increased epinephrin output play some part in the production of exophthalmos. The facts indicate that the thyroid may be involved in the production of, and is definitely concerned with, the physiological action of cyanides, possibly by directly or indirectly promoting detoxication. Very similar results have been reported by Schockaert and Loeb and by Friedman, produced by injections of ox anterior pituitary. The possibility of acetonitrile and pituitary extracts acting through the same mechanism must be borne in mind.—I. B.

Thyrotoxicosis. Meakins, J. C., M. Clin. North America, **16**: 751. 1932.

The two cases reported are of thyrotoxicosis during and immediately following operation. In the first case, the patient, a woman aged 47, had had a goiter since the age of 15, increased by four pregnancies. The patient had been self-Lugolized for one month previous to entry. Lugol's solution and digitalis therapy were given in the hospital for eight days. On admission the patient showed signs of thyrotoxicosis—tachycardia, forcible cardiac action, blood pressure 174/80, B.M.R. 176%. After operation there was a progressive rise in pulse rate, and a sharp rise in blood pressure. The evening of the day following the operation the pulse was 190 and the blood pressure had fallen to 130/90, signifying a distinct collapse in the circulation which might be interpreted as due to her fever, the body temperature being 41 degrees C. Auricular fibrillation had developed and her pulse decreased to 132, probably due to the effect of digitalis injections. The patient was in extremis and died a death typical of acute thyroid crisis. The second patient had noticed a lump appearing at the front of the neck ten years before at the age of 40. Three years before she had had acute pleurisy, following which thyrotoxic symptoms appeared. Two weeks before admission to the hospital she was given 30 drops of Lugo's solution daily. Pulmonary symptoms were present and there was a leukocytosis of 13,000. The patient continued in good postoperative condition for 15 hours, after which the pulse became rapid, respiration shallow, and restlessness occurred. The patient died five hours later. The opinion of the author is that the patient died of a widespread respiratory infection, of the character of acute bronchopneumonia, and not of thyrotoxicosis.—I. B.

Syphilis and thyroid disease with special reference to hyperthyroidism. Netherton, E. E., Am. J. Syphilis, **16**: 479. 1932.

The literature relating to the association of syphilis and thyroid disease has been reviewed. Sixty-two cases in which syphilis and thyroid disease were associated have been analyzed in an effort to evaluate the importance of syphilis as an etiologic factor in the production of thyroid dysfunction. Cases have been cited in which syphilis produced a symptom-complex which simulated that of hyperthyroidism and the opinion has been expressed that some of the cases reported in the literature are of this type. A careful examination to rule out neurosyphilis should be made in such cases. A case of probable gumma of the thyroid is reported. Antisyphilitic treatment should not replace surgical

intervention in cases of active hyperthyroidism in syphilitic individuals, as operation followed by antisyphilitic therapy will prevent the cardiac damage which may result from unnecessary delay. Syphilis does not interfere with the convalescence in these cases. Preoperative treatment is advisable but should not be too intensive. Patients having neurosyphilis associated with hyperthyroidism are poor surgical risks, especially if there is mental deterioration. Preoperative antisyphilitic treatment in these cases is indicated, as it is of definite value in cases of tabes dorsalis.—Author's Summary.

Distribution of iodine in the epithelial cells and the follicles of the thyroid; the distribution of iodine in the thyroid after treatment with epithelial cells and colloid substance as well as acid alcohol preparations of thyroid material (Ueber die Verteilung des Jods in den Epithelzellen und dem Follikelinhalte der Schilddrüse; Ueber den Einfluss der Darreichung von Epithelzellen-und Kolloidsubstanz der Schilddrüse sowie mit Salzsäurealkohol behandelten Thyreoideapraeparaten auf die Vertilung des Jods in der Schilddrüse). Nishikawa, S., Folia Endocrinol. Japon. **7**: 57. 1931.

The iodine content of the epithelial cells and of the colloid substance of rabbits was determined by the Baumann-Antenschen method. The epithelial and colloid substances of cattle thyroids were separated by Tatum's technique and the pulverized materials fed to rabbits. An acid alcohol extract of cattle thyroid and a sodium chloride solution of the residue was injected into rabbits. The feeding of the epithelial cell material caused a much greater increase of colloidal iodine than of epithelial iodine. The feeding of colloid substance decreased the weight of the thyroid, the iodine content of the epithelial cells and markedly increased the iodine of the colloid substance. The injection of the acid alcohol extract caused an increase in colloid iodine while an enormous decrease occurred in epithelial iodine. The injection of sodium chloride solution of the extract residue had no effect upon the iodine distribution of the thyroid.—J. Gagnon.

The problem of the thyroid gland and the metabolism of iodine (Das Schilddrüsenproblem und Jodstoffwechsel). Schittenhelm, A., Deutsche med. Wchnschr. **58**: 803. 1932.

Thyroxine has been resorbed in the duodenum after 12 hours and is secreted by the hyperthyreotics and normal individuals 85-92% in the faeces. In myxedema the thyroxine, like organic iodine, is secreted 68% in the urine. The blood iodine rises in Graves' disease, sinks in myxedema and thyrogenetic obesity. Iodine therapy lowers the organic iodine and raises the inorganic part, which has its depressing effect only in the peripheral organs. Di-iodotyrosine in doses of 10 mg. per day has the same effect but only for some weeks. The injections of "thyreogenetic hormone" of Paal raises the blood-iodine, raises the basal metabolism and gives a positive Reid-Hunt reaction. In Graves' disease a higher level of iodine was found in the diencephalon after injection of thyroxine, but not after ingestion of potassium iodide. Adrenaline raises the blood-iodine, too, if the thyroid gland is extirpated. In Graves' disease adrenaline lowers the blood iodine.—E. Kodicek.

Cabbage and goiter in Carpathian Ruthenia: A contribution to ethnic pathology. Suk, V., Anthropologie, **9**: 1. 1931. Abst., Ann. Int. Med. **6**: 451.

Goiter occurs endemically in many parts of the Carpathian Highlands; and the worst goiter centers are found in those poor villages where, during the unfavorable months of the year, more than two-thirds of the population live to a great extent on cabbage, with the addition of potatoes, corn bread and oats. How great a part cabbage, which is utilized as boiled sauerkraut, plays in the dietary is indicated by the fact that a family of eight members may pickle as much as 1100 pounds for their own use. Examination of the children in this region showed a much higher incidence of goiter in the village using excessive amounts of cabbage. This difference was especially evident among girls. Whereas 26.5% of all the girls examined were without goiter, only 7.9% of the girls in three villages using excessive amount of cabbage were free from thyroid enlargement. Of all the girls, 9.4% showed marked thyroid enlargement. For the three villages using much cabbage, the comparable figure was 15.8%.